



# Real-world data on the prevalence of BRCA1/2 and HRR gene mutations in patients with primary and metastatic castration resistant prostate cancer

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## Abstract

**Purpose** This study seeks to contribute real-world data on the prevalence of BRCA1/2 and HRR gene mutations in prostate cancer.

**Methods** We compiled sequencing data of 197 cases of primary and metastatic prostate cancer, in which HRR mutation analysis was performed upon clinical request within the last 5 years. All cases were analyzed using a targeted NGS BRCAness multigene panel, including 8 HRR genes (ATM, BRCA1, BRCA2, CDK12, CHEK2, FANCA, HDAC2, PALB2).

**Results** Our findings reveal a prevalence of potentially targetable mutations based on FDA criteria of 20.8%, which is comparable to the literature. However, the frequency of targetable BRCA2 mutations within our cohort was lower than reported for mCRPC and ATM and CHEK2 mutations were more prevalent instead. Thus, while 20.8% ( $n=38$ ) of the cases meet the criteria for olaparib treatment per FDA approval, only 4.9% ( $n=9$ ) align with the eligibility criteria according to the EMA approval.

**Conclusion** This study offers valuable real-world insights into the landscape of BRCA1/2 and HRR gene mutations and the practical clinical management of HRR gene testing in prostate cancer, contributing to a better understanding of patient eligibility for PARPi treatment.

**Keywords** Prostate cancer · PARPi · BRCA2 · HRR · Olaparib

## Introduction

In May 2020, the Food and Drug Administration (FDA) granted approval for olaparib (Lynparza) for patients diagnosed with metastatic castration-resistant prostate cancer

(mCRPC) possessing pathogenic or suspected pathogenic somatic or germline mutations in homologous recombination repair (HRR) genes. Specifically, this approval was extended to patients who had experienced disease progression following treatment with enzalutamide or abiraterone. Subsequently, the European Medicines Agency (EMA) endorsed olaparib for individuals harboring pathogenic or suspected pathogenic somatic or germline mutations in BRCA1/2 in November the same year. The phase 3 PROfound trial formed the basis for these regulatory decisions, demonstrated significant imaging-based progression-free survival (ibPFS) and overall survival benefits with olaparib in patients with mCRPC harboring BRCA1, BRCA2, and ATM mutations after disease progression on a next-generation hormonal agent [1] In addition, significant ibPFS and a trend towards prolonged overall survival was seen in patients harboring alterations in other HRR genes [1, 2].

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Furthermore, the PROpel trial's outcomes led to the approval of Olaparib in combination with abiraterone for mCRPC patients [3]. According to the EMA approval, BRCA1/2 and HRR gene testing is not mandated in this clinical context and chemotherapy must be contraindicated in these patients [4]. In contrast, proof of a BRCA1/2 mutation is required according to the FDA approval [5, 6]. In addition to the mutation test on tumor tissue, a mutation test on circulating tumor DNA (FoundationOne Liquid CDx; Foundation Medicine) was carried out in the PROpel trial, which allowed an increased detection of HRR gene alterations. [3] Other recent studies have led to approval of niraparib plus abiraterone and talazoparib plus enzalutamide in the same clinical setting [7, 8].

The prevalence of defects in DNA repair genes, particularly alterations in HRR genes, ranges from 19 to 33% among individuals with prostate cancer, depending on whether primary or metastatic tumor tissue is considered [9–11] BRCA2 alterations emerge as the most prevalent in metastatic disease [9–13].

An integrative assessment of 333 primary prostate cancers within the TCGA Research Network revealed inactivating alterations in DNA repair genes in approximately 19% of cases [11]. Notably, alterations in FANCD2 were most prevalent (7%), followed by ATM (4%), BRCA2 (3%), RAD51C (3%), CDK12 (2%), and BRCA1 (1%). While missense and truncating mutations were predominant for BRCA1, BRCA2, ATM, and CDK12, FANCD2 and

RAD51C exhibited mostly hemizygous and homozygous deletions.

The largest cohort of patients with mCRPC has been investigated by Robinson et al. [9] Using whole exome and transcriptome sequencing, targetable HRR alterations were found in 19.3% of the patients. BRCA2 alterations were most prevalent (12.7%) and 20% presented as homozygous deletions.

The TOPARP-A trial reported HRR gene alterations in 33% of cases in their cohort, with BRCA2 alterations being most common (14.3%) [14]. ATM alterations were found in 10.2% of patients, with diverse mutation types observed. The PROfound trial reported mutations predominantly in BRCA2, followed by ATM, CDK12, and few in CHEK2 [1].

The prevalence of germline mutations varies from 4.6% in localized disease to 16% in metastatic disease [9, 15, 16]. An unselected cohort of 692 patients with mCRPC demonstrated that about 11.8% harbored germline mutations in DNA repair genes, predominantly in HRR genes [15]. Of these, BRCA2 mutations were the most prevalent (5.3% of 11.8%). The PROREPAIR-B study found germline DNA repair mutations in 16% of 419 patients, primarily in BRCA2 (21%), ATM (12%), and BRCA1 (6%) [16].

Post the FDA and EMA approval of olaparib, numerous laboratories have initiated mutation analysis services for BRCA1/2 and HRR-related genes. This study aims to contribute real-world data on the prevalence of BRCA1/2 and HRR gene mutations in prostate cancer.

**Table 1** Clinicopathological data of the cohort

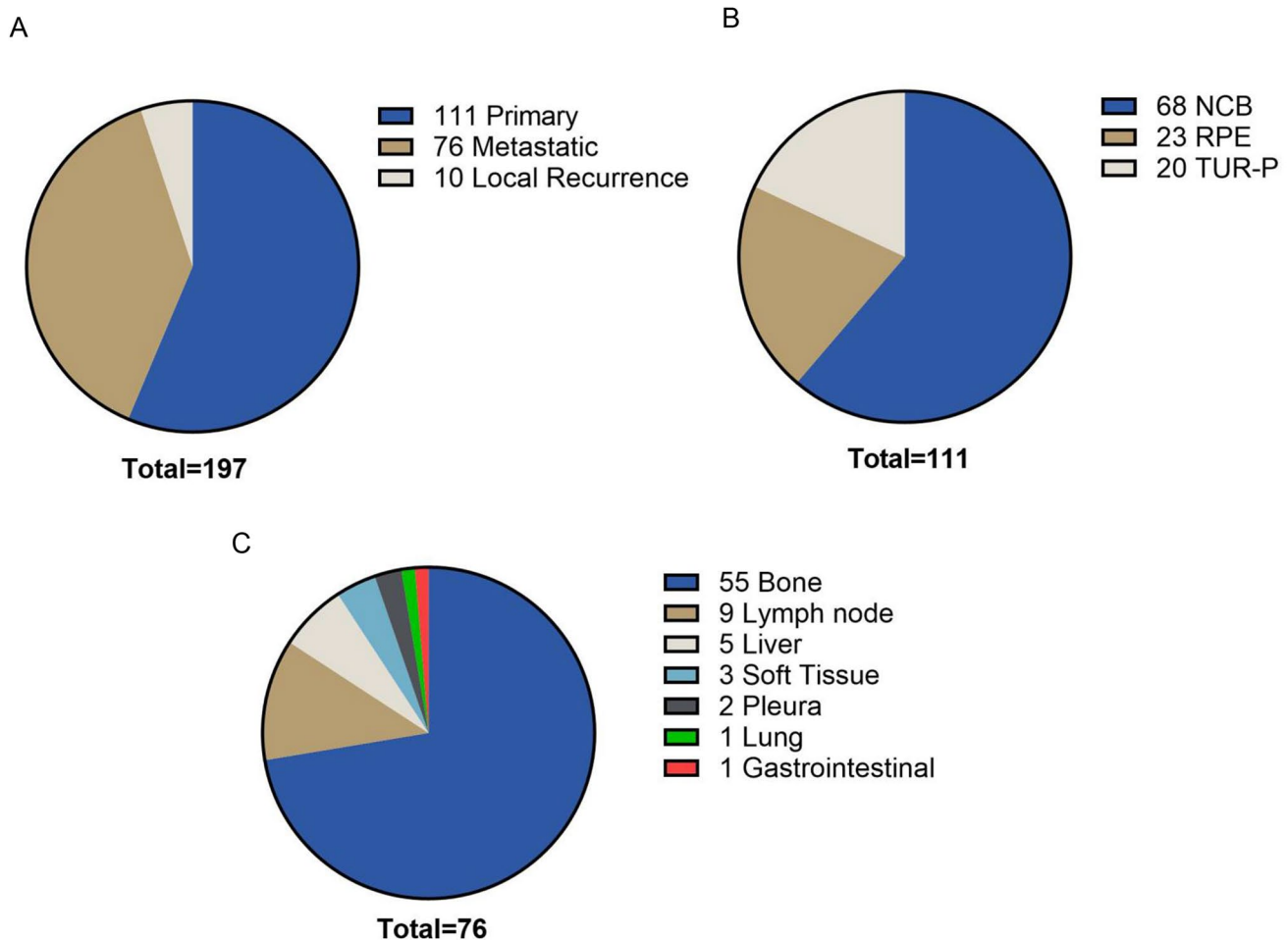
Clinical features	Finding (n = 197)
Age, median (range), years	71 (39–89)
Initial PSA, ng/ml, median (range)	30 (0.3–10.000)
Pathological parameters	
Grade Group at initial diagnosis, median (range)	4 (1–5)
Grade group 1, n (%)	3 (1.5%)
Grade group 2, n (%)	18 (9.1%)
Grade group 3, n (%)	12 (6.1%)
Grade group 4, n (%)	37 (18.8%)
Grade group 5, n (%)	97 (49.2%)
unknown, n (%)	29 (14.2%)
RPE parameters	
Organ-confined disease, n (%)	Finding (n = 55, 27.9%) 12 (21.8%)
Extrastatic extension, n (%)	13 (23.6%)
Seminal vesicle involvement, n (%)	29 (52.7%)
Infiltration of bladder, pelvic wall, rectum	1 (1.8%)
Lymph node positive, n (%)	21 (38.2%)
Positive margins, n (%)	28 (50.9%)
Tumor sample age, mean, years (range, sd)	2.1 (0–21, 3.7)
Time from initial diagnosis to HRR testing, years (range, sd)	5.4 (0–22, 5.2)

## Materials and methods

### Case selection and clinicopathological data of the cohort

197 cases of primary and metastatic prostate cancer were analyzed using a targeted NGS BRCAness multigene panel between September 2018 and December 2023 at the Institute of Pathology, University Hospital Bonn, upon clinical request. The clinicopathological data of the cohort is summarized in Table 1.

The median patient's age was 71 (range 39–89). The median initial PSA value was 30 ng/ml (range 0.3–10.000). The median ISUP grade at the initial diagnosis was 4 (range 1–5). The samples included primary tumor tissue, metastatic tumor tissue and tissue from local recurrences (Fig. 1). The majority of patients were clinically mCRPC at the timepoint of HRR testing (n = 171, 86.8%). For a subset of the patients a recent tumor sample obtained in the setting of mCRPC was analyzed (40.1% (n = 79)). For the remaining patients, primary tissue from the initial diagnosis was investigated.



**Fig. 1** The distribution of tumor samples tested for HRR alterations. (A) Primary tumor samples were the preferred type of tumor tissue tested for HRR alterations ( $n=111$ ), followed by metastatic tumor tissue ( $n=76$ ) and tumor tissue from local recurrences ( $n=10$ ). (B) Needle core biopsies (NCB) from the initial diagnosis of prostate cancer were the preferred material tested for HRR alteration ( $n=68$ ),

followed by radical prostatectomy specimen (RPE) ( $n=23$ ) and transurethral resection specimen (TUR-P) ( $n=20$ ). (C) Bone metastases were the most common material tested for HRR alterations ( $n=55$ ), followed by distant lymph node metastases ( $n=9$ ), liver metastases ( $n=5$ ), soft tissue metastases ( $n=3$ ), pleural metastases ( $n=2$ ). Lastly, one lung metastasis and one gastrointestinal metastasis were analyzed

Pathological data from radical prostatectomy specimen was available for 55 patients. 42 (76.4%) patients showed non-organ-confined disease, 21 (38.2%) showed positive lymph nodes and 28 (50.9%) had positive resection margins. The mean tumor sample age was 2.1 years (range 0–21). The mean time from the initial diagnosis to molecular testing was 5.4 years (range 0–22).

All data was acquired prospectively during patient care, rendering a specific ethics votum not necessary.

### Sample preparation, DNA isolation, sequencing and data analysis

Suitable tumor areas were grossly dissected after histological review of the slides by a board certified pathologist and the epithelial cellularity was recorded. DNA extraction was conducted with the Maxwell RSC DNA FFPE

Kit (Promega, Madison, Wisconsin, US). Next generation sequencing was performed using a QIAseq™ targeted DNA BRCAness custom panel (Qiagen, Hilden, Germany) including 8 genes involved in homologous recombination repair as follows: ATM, BRCA1, BRCA2, CDK12, CHEK2, FANCA, HDAC2, PALB2. All coding sequences were analyzed comprising a total of 38,450 bp. Generation of multiplex amplicons and library preparation including unique molecular identifiers was performed according to the manufacturer's recommendations. Next generation sequencing was performed on a MiSeq sequencer with a coverage of > 100 (Illumina, San Diego, US). Data was analyzed with the CLC Genomics Workbench/Server (Qiagen Bioinformatics, Hilden, Germany). Coding-synonymous variants, intronic variants not involving consensus splice sites and variants with a population allele frequency of > 1% were filtered. Variants called benign in databases were

not reported. Pathogenic and likely pathogenic mutations with an allele frequency of  $\geq 5\%$  were reported. Classification of variants was performed according to the following databases: dbSNP, ExAC, COSMIC, ClinVar, OncoKB, UMD-BRCA1/2 Databases (University of Utah BRCA1/2 databases).

### Statistical analysis and software

Statistical analysis was performed using Prism, Version 10.2.2 (GraphPad Software, Boston, US). Chi-square test was used for comparing the prevalence of mutations in metastatic and primary tumor tissue. Graphs were generated with Prism, Version 10.2.2 (GraphPad Software, Boston, US).

### Results

In this study, we compiled BRCA1/2 and HRR sequencing data of 197 cases of primary and metastatic prostate cancer.

The distribution of tumor tissue tested revealed a predominant analysis of primary tumor tissue ( $n = 111$ , 56.3%) in contrast to metastatic tumor tissue ( $n = 76$ , 38.6%) and tumor tissue from local recurrences ( $n = 10$ , 5.1%) (Fig. 1A). The preferred sources for primary tumor testing included prostate needle core biopsies ( $n = 68$ , 34.5%), followed by radical prostatectomy (RPE) specimens ( $n = 23$ , 11.7%) and transurethral resection (TUR) specimens ( $n = 20$ , 10.2%) (Fig. 1B).

Bone metastases ( $n = 55$ , 27.9%) were the most common metastatic tumor tissue followed by distant lymph node metastases ( $n = 9$ , 4.6%), hepatic metastases ( $n = 5$ , 2.5%) and infrequent metastatic sites such as pleura, lung, gastrointestinal tract or soft tissue metastases (in total  $n = 7$ , 3.6%) (Fig. 1C).

The majority of patients were clinically mCRPC at the timepoint of HRR testing ( $n = 171$ , 86.8%). However, only in a subset of those patients a recent tumor sample obtained in the setting of mCRPC was analyzed (40.1% ( $n = 79$ )). For the remaining patients, primary tissue from the initial diagnosis, such as needle core biopsies, RPE specimen and TUR specimen, was investigated, which is considered hormone-sensitive tumors.

A subset of cases ( $n = 14$ , 7.1%) exhibited insufficient DNA quality. Intriguingly, almost all ( $n = 13$ ) instances of insufficient quality pertained to primary tumor samples. The mean sample age of the primary samples with insufficient DNA quality was greater compared to the mean sample age of the primary samples with sufficient DNA quality (8.1 years vs. 3.0 years). Therefore, the insufficient quality can likely be attributed to the sample age. In contrast, metastatic

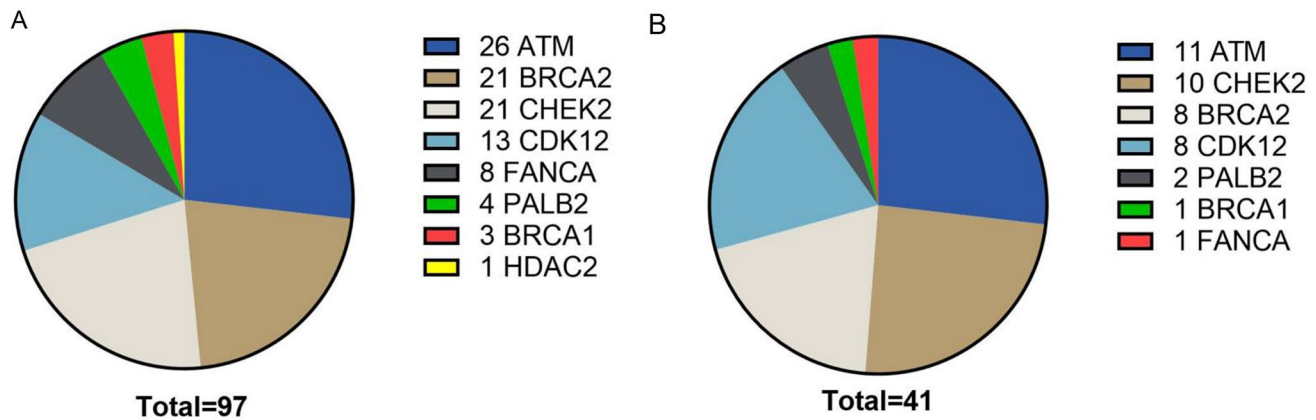
tissue samples uniformly exhibited adequate sequencing quality. One case of a local recurrence, sampled via needle core biopsy, showed insufficient quality as well.

Among the 183 cases subjected to comprehensive variant analysis, 79 cases (43.2%) manifested at least one suspected benign variant, variant of unknown significance, suspected pathogenic mutation or pathogenic mutation. Unambiguous benign variants were not reported. The distribution of cases with mutations indicated a prevalence of single mutations in 55 cases (30.0%), double mutations in 17 cases (9.3%), and triple mutations in 7 cases (3.8%), accounting for a total of 110 mutations.

The mutations, including suspected benign variants, variants of unknown significance, suspected pathogenic or pathogenic mutations, were distributed among the cases as follows (Fig. 2A): 26 showed ATM mutations (14.2%), 21 showed BRCA2 mutations (11.5%), 21 showed CHEK2 mutations (11.5%), 13 showed CDK12 mutations (7.1%), 8 showed FANCA mutations (4.4%), 4 showed PALB2 mutations (2.2%), 3 showed BRCA1 mutations (1.6%), and 1 showed a HDAC2 mutation (0.5%). Notably, slightly less than a half of these mutations (43.6%,  $n = 48$ ) were deemed pathogenic or suspected pathogenic according to pertinent databases, suggesting potential targetability. As anticipated, the prevalence of pathogenic or suspected pathogenic mutations was higher in metastatic tumor tissue compared to primary tumor tissue (25.0% vs. 19.4%), although this was not statistically significant ( $p$ -value 0.37). No pathogenic or suspected pathogenic mutations could be detected in tumor tissue from local recurrences ( $n = 9$ ). Further analysis discerned that pathogenic or suspected pathogenic mutations were distributed as follows (Fig. 2B): 11 ATM mutations (6.0%), 10 CHEK2 mutations (5.5%), 8 BRCA2 mutations (4.4%), 8 CDK12 mutations (4.4%), 2 PALB2 mutations (1.1%), 1 FANCA mutation (0.6%), and 1 BRCA1 mutation (0.6%). No pathogenic or suspected pathogenic HDAC2 mutations were identified. In total, 38 out of 183 cases (20.8%) exhibited a potentially targetable mutation, while the remainder showcased variants of unknown significance ( $n = 37$ , 20.2%) or suspected benign variants ( $n = 4$ , 2.2%).

### Discussion

The positive outcomes observed in the PROfound trial have prompted a clinical imperative for testing BRCA1/2 and homologous recombination repair (HRR) gene mutations in patients with metastatic castration-resistant prostate cancer (mCRPC) [1]. The prevalence of HRR mutations in prostate cancer has been documented in numerous studies, demonstrating variations depending upon the origin of the tissue, whether primary or metastatic and the stage of disease



**Fig. 2** The distribution of HRR gene mutations. (A) Depiction of all HRR mutations found, including suspected benign variants, variants of unknown significance, suspected pathogenic and pathogenic mutations. ATM ( $n=26$ ) mutations were most prevalent, followed by mutation in BRCA2 ( $n=21$ ), CHEK2 ( $n=21$ ), CDK12 ( $n=13$ ), FANCA ( $n=8$ ), PALB2 ( $n=4$ ), BRCA1 ( $n=3$ ) and HDAC2 ( $n=1$ ). (B)

Depiction of suspected pathogenic and pathogenic HRR mutations. ATM ( $n=11$ ) mutations were most prevalent, followed by mutation in CHEK2 ( $n=10$ ), BRCA2 ( $n=8$ ), CDK12 ( $n=8$ ), PALB2 ( $n=2$ ), BRCA1 ( $n=1$ ) and FANCA ( $n=1$ ). No suspected pathogenic or pathogenic mutations in HDAC2 were found

[9–12, 14]. A large study on primary hormone-sensitive prostate cancer documented targetable HRR alterations in about 19% of cases, while the prevalence in mCRPC ranges from 19 to 33% [9–11, 14]. Herein, we present real-world data derived from the analysis of 197 prostate cancer cases over a 5-year period within a single institution.

Within our cohort, the prevalence of pathogenic or suspected pathogenic mutations was determined to be 20.8% ( $n=38$ ), in accordance with published data. However, in contrast to published data, the distribution of the mutations differed substantially. Our findings reveal a predominance of targetable mutations in ATM, succeeded by mutations in CHEK2 and BRCA2. Thus, targetable BRCA2 mutations were less frequently identified in our cohort. According to the literature, the prevalence of BRCA2 alterations in primary prostate cancer is significantly lower than that in mCRPC [9, 11]. The cohort presented here consists of a mixture of primary and metastatic castration-resistant tumors, which is a valid explanation for the lower prevalence of BRCA2 mutations. In concordance to the literature, BRCA1 mutations were found in less than 1% of all cases. In the context of olaparib treatment, this signifies that 20.8% ( $n=38$ ) meet the criteria for treatment per FDA approval, whereas only 4.9% ( $n=9$ ) align with the eligibility criteria for olaparib treatment according to EMA approval.

The prevalence of ATM mutations in our study is similar to that described in the literature. In mCRPC, ATM mutations are present in 5–8%, while the prevalence is two-fold lower in primary prostate cancer [9, 11, 15, 17]. ATM germline mutations are potential prognostic biomarkers because they are enriched in patients with lethal and high grade disease [18, 19]. However, this association has not been verified for somatic mutations. In addition to its role as a potential

prognostic biomarker, ATM status was also described as a predictive biomarker regarding treatment response to olaparib in the initial studies [20, 21]. Yet, recent studies on PARP inhibition therapy in mCRPC indicate, that the response rate of ATM mutated tumors is lower than that of BRCA2 mutated tumors [1, 22–26].

Our data also sheds light on practical clinical management involving this novel diagnostic test. It is the metastatic tumor manifestation that drives disease progression in prostate cancer. In accordance with the published data, the prevalence of potentially treatment relevant mutations in our cohort was slightly higher in metastatic tumor tissue compared to primary tumor tissue (19.4% vs. 25.0%), although this was not statistically significant. Furthermore, primary tumor tissue exhibited greater instances of insufficient quality, likely attributable to inadequate DNA quality. Consequently, it advises to consider harvesting metastatic tumor tissue as the preferred material for optimal treatment planning. Despite this, within our cohort of 197 cases, mutation analysis was predominantly conducted on primary tumor tissue, possibly because metastatic tumor biopsy for molecular testing is still not common practice. Also, as clinicians are aware of the fact, that in nearly half of the cases HRR alterations constitute germline defects, they prefer to resort to the already existing biopsy material. However, the data of this study suggests that an additional biopsy of a bone metastasis has the potential benefit of obtaining tumor tissue with an adequate DNA quality and a slightly higher likelihood of detecting a targetable mutation.

A limitation of our study lies in the absence of data on genomic deletions, which are challenging to reliably detect using next-generation sequencing. This might also account

for the comparatively lower number of alterations identified, particularly in BRCA2.

In conclusion, this unicentric analysis of BRCA1/2 and HRR gene mutations in prostate cancer, analyzed over a 5-year period, found a lower prevalence of BRCA2 mutations than previously reported: only 4.9% are deemed eligible for olaparib treatment as per EMA approval.

**Author contributions** Moritz Hommerding, Oliver Hommerding, Glen Kristiansen: Project development, data collection, data analysis, manuscript writing and manuscript editing. Marit Bernhardt, Tobias Kreft, Christine Sanders, Verena Tischler, Patrick Basitta, Natalie Pelusi, Anna-Lena Wulf: data collection and data analysis, manuscript editing. Carsten-Henning Ohlmann, Jörg Ellinger, Manuel Ritter: data collection, manuscript editing.

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## Declarations

**Conflict of interest** The authors declare no conflict of interest.

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