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Prostate Cancer

Feasibility of Next-generation Sequencing of Liquid Biopsy (Circulating Tumor DNA) Samples and Tumor Tissue from Patients with Metastatic Prostate Cancer in a Real-world Clinical Setting in Germany

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Abstract

Background and objective: With European Medicines Agency approval of PARP inhibitors in metastatic castration-resistant prostate cancer and ongoing trials in metastatic hormone-sensitive prostate cancer, detection of genetic alterations in *BRCA1/2* and other homologous recombination repair genes has gained an important role. Our aim was to investigate the feasibility and comparability of comprehensive next-generation sequencing (NGS) of liquid biopsy (LB; circulating tumor DNA) and tumor tissue (TT) samples in a real-world clinical setting.

Methods: The study cohort consisted of 50 patients with metastatic prostate cancer (mPC) who had TT NGS performed for *BRCA1/2* alterations and consent for additional LB NGS. The Oncomine Comprehensive Assay v3 (Thermo Fisher Scientific, Waltham, MA, USA) was used for TT NGS. The Guardant360 83-gene assay (Guardant Health, Palo Alto, CA, USA) was used for LB NGS, including all types of somatic alterations, microsatellite instability, and blood tumor mutational burden. We calculated *BRCA1/2* alteration rates and the negative percentage agreement (NPA) and positive percentage agreement (PPA) between TT and LB results.

Key findings and limitations: TT NGS was successful in 44/50 patients (88%), with pathogenic *BRCA1/2* alterations detected in four (9%). LB NGS was successful in all 50 patients (100%), with *BRCA1/2* alterations detected in ten (20%). In a subgroup analysis for the 44

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patients with successful TT NGS, NPA was 85% and PPA was 50%. The median time between TT sample collection and blood sampling for NGS was 132 wk (IQR 94–186). The limited sample size and differences in the time of NGS assessment are limitations.
Conclusions and clinical implications: LB NGS resulted in a higher detection rate for *BRCA1/2* alterations in comparison to conventional TT NGS (20% vs 9%). Ideally, *BRCA1/2* testing should be based on both approaches to identify all patients with mPC eligible for PARP inhibitor therapy.
Patient summary: Our study shows that genetic tests for both tumor tissue and blood samples results in higher rates of detection of *BRCA1/2* gene alterations in patients with metastatic prostate cancer.
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1. Introduction

The treatment landscape for metastatic prostate cancer (mPC) has seen remarkable evolution over the last decade owing to the approval of various systemic agents for metastatic hormone-sensitive PC (mHSPC) and castration-resistant PC (mCRPC) [1–14]. Most recently, the European Medicines Agency (EMA) approved PARP inhibitors for mCRPC on the basis of results from two phase 3 randomized trials (PROfound, NCT02987543; PROpel, NCT03732820) [15–17]. In these trials, patients with alterations in homologous recombination repair (HRR) genes such as *BRCA1/2* and *ATM* were especially sensitive to PARP inhibitors, as evidenced by better median progression-free survival [15–17]. Consequently, detection of such gene alterations in mPC is crucial. Although tumor tissue (TT) represents the current gold standard for next-generation sequencing (NGS), high test failure rates of up to 30% have been reported in previous studies [15,17–19]. Liquid biopsy (LB; circulating tumor DNA [ctDNA]) NGS has demonstrated promising results for detection of HRR gene alterations, but the data available are predominantly from trial settings [20]. To address this lack of real-world data, we investigated the feasibility and comparability of LB and TT NGS for detection of HRR gene alterations in 50 patients with mPC. For patients for whom a TT NGS result was available, we compared the result to LB findings from the Guardant360 83-gene assay (Guardant Health, Palo Alto, CA, USA).

2. Patients and methods

2.1. Study population

From March 2021 to August 2022, patients with mPC treated at our tertiary care center who were either eligible for or had already undergone TT NGS were offered an LB (ctDNA) NGS assay in addition to regular blood tests. Initially, only patients with mCRPC were eligible, but the eligibility criteria were then expanded to mHSPC on the basis of new data for PARP inhibitors in this setting. The study was approved by the University Cancer Center Frankfurt institutional review board and the ethics committee at University Hospital Frankfurt. All patients included in the study gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association.

2.2. NGS for TT samples

All assays used for TT NGS tested at least *BRCA1* and *BRCA2* gene alterations. Because of differences in the timing and location of NGS for TT samples, different assay panels were used (Supplementary Table 1). In most cases (74%), the Oncomine Comprehensive Assay v 3 panel (ThermoFisher Scientific, Waltham, MA, USA) was used. Tissue from the prostate or from metastatic sites was accepted for evaluation.

2.3. NGS for LB samples

For LB analysis, the Guardant360 v2.12 83-gene assay (Guardant Health) was used for all samples. This is a research-use NGS assay performed on peripheral blood from cancer patients for a panel of 83 genes (reportable range) to identify genomic alterations in cancer-associated somatic variants with high sensitivity. Cell-free DNA was extracted from plasma, and genomic alterations were analyzed via parallel sequencing of amplified target genes. All genes were examined for single nucleotide variants (SNVs) and insertions/deletions (InDels). In addition, 19 genes were examined for copy number amplifications and 11 genes for fusions. Microsatellite instability (MSI) was qualitatively assessed for all tumor types by evaluating somatic changes in the length of 1329 microsatellites (ie, repetitive sequences) on the Guardant v2.12 panel.

2.4. Definition of mCRPC

In accordance with the European Association of Urology guidelines, mCRPC status was defined as castrate serum testosterone <50 ng/dl (<1.7 nmol/l) plus either (1) biochemical progression (three consecutive prostate-specific antigen [PSA] increases at least 1 wk apart resulting in two 50% increases over the nadir and PSA >2 ng/ml) or (2) radiologic progression with the appearance of new lesions (either two or more new bone lesions on bone scintigraphy or 1 soft-tissue lesion) according to Response Evaluation Criteria in Solid Tumors [1].

2.5. Statistical analyses

Descriptive statistics include the frequency and proportion for categorical variables, and the median and interquartile range (IQR) for continuous variables. Descriptive patient characteristics and NGS data were tabulated for the overall cohort. For patients with (successful) data for both TT and LB NGS, negative percent agreement (NPA) and positive percent agreement (PPA) values were assessed. NPA was defined as the number of patients without a *BRCA1/2* gene alteration on both TT and LB NGS. PPA was defined as the number of patients with a *BRCA1/2* gene alteration on both TT and LB NGS. Since *BRCA1/2* copy number variations (CNVs) can also be detected in LB samples, analyses were performed with and without considering *BRCA1/2* CNVs.

BRCA1/2 gene alteration rates using combined TT and LB NGS information NGS were calculated, again with and without inclusion of *BRCA1/2* CNVs.

Finally, with regard to the HRR genes tested in the PROpel study, the following HRR-related alterations were examined via LB NGS: *BRCA1, BRCA2, ATM, CDK12, CHEK2, FANCL/FANCA, PALB2,* and *RAD51D*. Owing to the heterogeneity of the TT NGS panels used, no comparison was made between TT and LB NGS results of HRR gene alterations other than *BRCA1/2*. R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses [21].

3. Results

3.1. Patient characteristics

In the overall cohort, most patients (72%) had primary mPC. The median age was 65 yr (IQR 57–72) and median initial PSA was 74 ng/ml (IQR 16–307). Some 42 patients (86%) had a Gleason score of 8–10 at diagnosis. At the time of blood collection for LB, 38 patients (76%) had mCRPC and 12 (24%) had mHSPC (Table 1).

3.2. TT and LB NGS

For NGS analysis of TT samples, primary prostate cancer tissue was used in 63%, metastatic tissue in 18%, and carcinoma manifestation of unknown location in 18% (Table 2). The median time from TT sample collection and NGS analysis was 42 wk (IQR 8–120). Of all 50 TT NGS assays performed in the current study, 44 (88%) were technically successful and had data available for further analysis (Table 2). For LB NGS analyses, the blood sample for testing was collected from all 50 patients during a regular follow-up appointment. The median time between blood collection for LB NGS and the availability of the results was 11 d (IQR 10–13). The median time between TT sample collection and blood collection for LB NGS was 132 wk (IQR 94–186). All 50 LB analyses were technically successful. The tumor mutational burden (TMB) was evaluable in 33 LB samples (66%), with a median TMB of 7.8 mutations/megabase (IQR 5.7–11.5).

3.3. BRCA1/2 gene alterations

TT NGS revealed pathogenic *BRCA1/2* alterations in 4/44 patients (9%). Specifically, one patient had a pathogenic *BRCA1* alteration, two patients had a pathogenic *BRCA2* alteration, and one patient had both *BRCA1* and *BRCA2* alterations.3

LB NGS revealed *BRCA1/2* alterations (including CNVs) in ten of 50 patients (20%). These comprised *BRCA1* alterations in three patients (6%) and *BRCA2* alterations in seven patients (14%).

In a subgroup analysis (n = 44) that excluded patients with unsuccessful TT NGS, the rate of *BRCA1/2* alterations was 9% (four of 44) for TT NGS and 18% (eight of 44) for LB NGS (including CNVs), yielding NPA of 85% (34/40) and PPA of 50% (two of four; Fig. 1A). When *BRCA1/2* CNVs were excluded, the rate of *BRCA1/2* alterations was also 9% (four of44) for LB NGS, yielding NPA of 95% (38/40) and PPA of 50% (two of four; Fig. 1B).

According to results for both LB and TT NGS (regardless of technical success) in the entire study cohort, the combined rate of *BRCA1/2* alterations including CNVs was 24% (12/50; Fig. 2A). When CNVs were excluded, the combined *BRCA1/2* alteration rate was 12% (six of 50; Fig. 2B).

3.4. HRR gene alterations in LB NGS

According to LB NGS (n = 50), the overall prevalence of at least one alteration in the HRR genes *BRCA2, BRCA1, ATM, CDK12, CHEK2, FANCA, PALB2*, and *RAD51D*, including BRCA1/2 CNVs, was 40% (20/50). When *BRCA1/2* CNVs were excluded, the frequency of HRR gene alterations was 36% (18/50).

Table 1 – Characteristics of the 50 patients with metastatic prostate cancer who had NGS performed for both tumor tissue and liquid biopsy samples

Parameter	Patients	Result
Median age at diagnosis, yr (IQR)	50	65 (57–72)
Median PSA at diagnosis, ng/ml (IQR)	44	74 (16–307)
ECOG PS at score diagnosis, *n* (%)	44	
0		32 (73)
1		11 (25)
2		1 (2.3)
cM stage at diagnosis, *n* (%)	50	
M0 (metachronous)		13 (26)
M1 (synchronous)		36 (72)
Mx (unknown)		1 (2.0)
Metastatic status, *n* (%)	50	
Hormone-sensitive		12 (24)
Castration-resistant		38 (76)
Gleason sum score, *n* (%)	49	
6		0 (0)
7		7 (14)
8–10		42 (86)
Combined cT/pT stage, *n* (%)	50	
T1		8 (16)
T2		6 (12)
T3		20 (40)
T4		9 (18)
Unknown		7 (14)
Local therapy, *n* (%)	50	
None		25 (50)
Radiotherapy		6 (12)
Radical prostatectomy		19 (38)

IQR = interquartile range; cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen.

Table 2 – NGS characteristics of TT and LB samples from patients with metastatic prostate cancer

Parameter	Patients	Result
Median time from TT sample collection to TT NGS, wk (IQR)	43	42 (8–120)
Median time from TT sampling to LB sampling for NGS, wk (IQR)	49	132 (94–186)
Origin of tumor sampled, *n* (%)	49	
Prostate		31 (63)
Metastasis		9 (18)
Unknown		9 (18)
Successful TT NGS, *n* (%)	50	44 (88)
Successful LB NGS, *n* (%)	50	50 (100)
TMB evaluable in LB, *n* (%)	50	33 (66)
Median TMB in LB, mutations/megabase (IQR)	33	7.8 (5.7–11.5)

IQR = interquartile range; LB = liquid biopsy; NGS = next-generation sequencing; TMB = tumor mutational burden; TT = tumor tissue.

4. Discussion

This molecular diagnostic study highlights the differences between LB and TT NGS assays for detection of *BRCA1/2* gene alterations. In contrast to the TT analyses, LB analyses were evaluable in all our patients and showed a higher rate of pathogenic alterations. Most of the additional LB alterations identified were gene copy alterations (CNVs). LB might overcome the challenges associated with repeat biopsy and biopsy at disease progression, as well as tumor

(A)

		LB *BRCA2* and/or *BRCA1* alteration			
		Negative	Positive	Total	
TT *BRCA2* and/or *BRCA1* alteration	Negative	34	6	40	NPA: 34/40 (85%)
	Positive	2	2	4	PPA: 2/4 (50%)
	Total	36	8	44	

(B)

		LB *BRCA2* and/or *BRCA1* alteration			
		Negative	Positive	Total	
TT *BRCA2* and/or *BRCA1* alteration	Negative	38	2	40	NPA: 38/40 (95%)
	Positive	2	2	4	PPA: 2/4 (50%)
	Total	40	4	44	

Fig. 1 – Concordance between TT and LB NGS for *BRCA2* and/or *BRCA1* alterations among 44 patients (A) including and (B) excluding copy number variations. LB = liquid biopsy; NGS = next-generation sequencing; NPA = negative percentage agreement (percentage of patients without *BRCA2/1* alterations on both TT and LB NGS); PPA = positive percentage agreement (percentage of patients with *BRCA2/1* alterations on both TT and LB NGS); TT = tumor tissue.

heterogeneity, including the difficulty in obtain valuable material from bone metastases.

Subgroup analyses in PROpel and PROfound revealed a survival benefit for patients with HRR gene alterations, especially *BRCA1/2* alterations, highlighting the critical role of detection of these alterations in patients with mPC. To date, TT NGS is the gold standard for evaluating HRR gene alterations. However, data for NGS of ctDNA have shown promising results. Because current knowledge regarding LB NGS is predominantly based on results from phase 3 trials, we addressed this lack of real-world data and investigated the feasibility and comparability of LB and TT NGS in 50 patients with mPC patients, with some notable results.

First, failure rates for NGS testing differed substantially between TT and LB (Table 2). Among the 50 TT NGS assays, only 88% were successful (Table 2). Consequently, for a non-negligible number of patients, identification of HRR gene alteration status for treatment selection would not be possible from TT NGS alone. This "failure" rate is in line with rates previously reported for TT NGS. For example, Hussain et al [19] tested TT samples from more than 4000 patients and obtained successful NGS results for 69%. Similarly, Clarke et al [17] reported failure rates of 32–33% for TT NGS in PROpel. Even though the reasons for failure may be manifold (amount/quality of tumor tissue), harvesting of an additional "fresh" TT sample would expose the patient to potential procedure-related complications and a delay in identification of HRR gene status. Therefore, failed TT NGS represents a dilemma for both patients and clinicians. By contrast, the success rate for LB NGS was 100% (Table 2) and NGS of ctDNA resulted in information on HRR gene alterations for all patients. It is of note, however, that TMB was only evaluable in 66%, with a median TMB of 7.8 mutations/megabase (IQR 5.7–11.5).

Second, *BRCA1/2* gene alterations were identified in 9% (four of 44) of TT and 20% (ten of 50) of LB analyses. These detection rates fall within the upper range of rates previously reported for *BRCA2* and *BRCA1* gene alterations. For example, Clarke et al [17] reported lower rates of *BRCA1* (0.8–2.3%) and *BRCA2* (8.8–9.5%) alterations using aggregate data that included both TT and LB NGS results for a cohort of patients with mCRPC. The possibility of patient selection bias in the current study cannot be excluded, which could lead to an artificially elevated *BRCA1/2* gene mutation rate. Because our study population was selected in a tertiary referral center, the cohort may have a more aggressive PC phenotype and thus could have a higher rate of *BRCA1/2* gene alterations. It is important to note that a certain percentage of *BRCA1/2* gene alterations we detected via LB were CNVs (Supplementary Table 2). Consistent with this result, Barnett et al [22] found that ~30% of *BRCA2* alterations in mCRPC in previous studies were due to copy number loss [23,24]. These findings underline the importance and value of additional NGS testing besides TT-based approaches [25]. The EMA approval of olaparib explicitly refers to mutations (substitutions, insertions, deletions) and not to CNVs, which cannot be detected via tissue-based NGS using formalin-fixed paraffin material. CNV calling was performed in PROfound, but the impact of different types of genomic *BRCA1/2* changes (SNVs and InDels vs CNVs) is not included in the PROfound study report. Therefore, we present data for our comparison with differentiation for CNVs. It remains to be seen whether CNVs will be predictive of response to olaparib in our study population; we are currently investigating *BRCA1/2* alteration status via LB for numerous additional patients with mPC treated with olaparib.

Third, we assessed concordance between TT and LB NGS in a subgroup analysis for the 44 patients with successful TT NGS. In this subgroup, the rate of *BRCA1/2* gene alterations was 9% (four of 44) for TT NGS and 18% (eight of 44) for LB NGS (Fig. 1A); thus, the discrepancy between TT and LB results was very high. Specifically, the PPA for LB NGS ver-

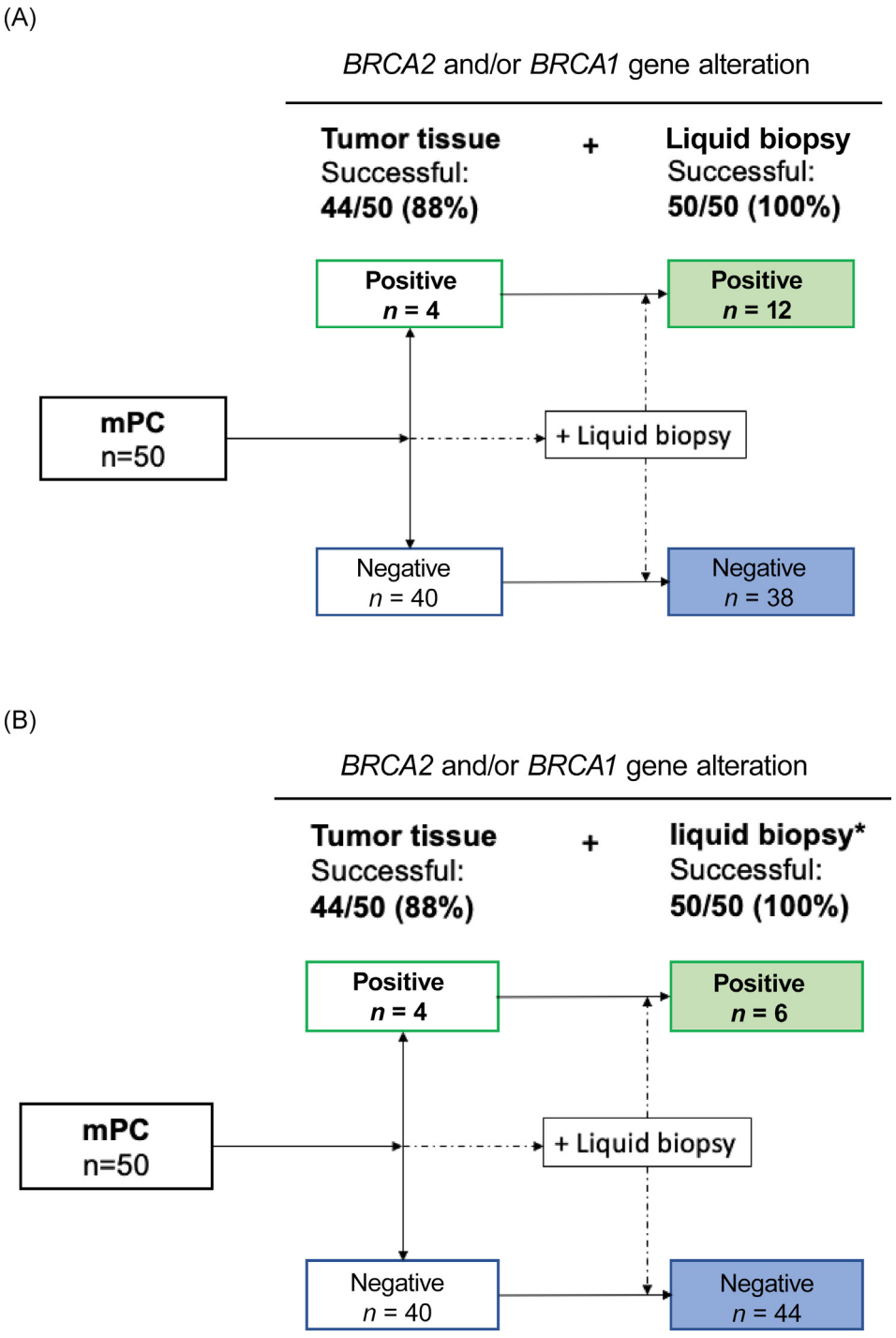


Fig. 2 – Detection rates for *BRCA2* and/or *BRCA1* alterations via next-generation sequencing of tumor tissue (*n* = 44) and liquid biopsy samples (*n* = 50; Guardant360 assay) for alteration panels (A) including and (B) excluding copy number variations. mPC = metastatic prostate cancer.

sus TT NGS was only 50%. In other words, LB NGS failed to detect *BRCA1/2* alterations in two patients with positive TT NGS results. By contrast, LB NGS identified *BRCA1/2* alterations in six of 40 patients with wild-type *BRCA1/2* results on TT NGS, resulting in NPA of 85% (Fig. 1A). However, our PPA and NPA values may be distorted by the large time difference between TT sampling and blood sampling for LB (median 132 wk, IQR 94–186), which could explain the lower values in comparison to previous studies [17,25,26]. For example, Chi et al [25] compared TT NGS results from the PROfound study to ctDNA sequencing (*BRCA2, BRCA1, ATM*) for blood samples in a retrospective analysis of TT and LB NGS concordance (*n* = 491). Using TT as the reference, the authors found PPA of 81% and NPA of 92%. It should be noted that blood samples were collected at the time of screening for enrollment [25].

From a clinical perspective, use of only one NGS assay would inevitably miss patients with gene alterations who would have been identified by the other test. Consequently, use of both testing approaches would yield the highest

chance of identifying most HRR gene alterations. With emerging evidence that patients with mCRPC and HRR gene alterations benefit the most from PARP inhibition, identification of these patients with high certainty is of fundamental importance. This also applies to treatment options other than PARP inhibitors that have equivalent efficacy in mCRPC. For our study cohort, aggregated results for both TT and LB NGS resulted in an overall rate of *BRCA1/2* gene alterations of 24%, supporting the concept of using both NGS approaches in real-world clinical settings. Consistent with our findings, Armstrong et al. [17,27], citing the PROpel cohort, reported in the group of patients with unsuccessful TT NGS (n = 261), NGS of ctDNA was successful in more than 93%, significantly increasing the possibility of detecting gene alterations in the cohort of mCRPC patients.

Our study is not free of limitations. First, the sample size and therefore the statistical analyses are limited. Second, different timings for TT and blood collection for NGS could represent a bias affecting the concordance rate between TT and LB rates for *BRCA1/2* alterations. Both prostatic and metastatic tissue was used for TT NGS. However, because of sample size limitations, no analysis of the success rate for primary tumor versus metastatic sites was possible. In addition, because of the study design, different TT NGS panels were used and there was no subsequent independent pathology review. Therefore, the TT NGS results may have been influenced by differences in detection capability for gene alterations. It is of note, however, that the majority of TT NGS (74%) analyses were performed with the same NGS assay. Third, the study design did not allow differentiation between germline and sporadic gene alterations. Fourth, the study design may have led to selection bias. Finally, data on response rates in terms of progression-free and overall survival are currently not available.

5. Conclusions

Combining NGS of LB and tumor tissue resulted in a higher detection rate for *BRCA1/2* alterations in comparison to NGS of tumor tissue alone (18% vs 9%). Therefore, testing for *BRCA1/2* alterations should be based on both approaches to identify all patients with metastatic prostate cancer who are eligible for PARP inhibitor therapy. LB samples can overcome tumor heterogeneity and the complexity of performing biopsy after disease progression or in cases with multiple disease sites. The short turnaround time for LB results is an additional clinical benefit.

Author contributions: Philipp Mandel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mandel, Hoeh, Humke, Chun, Wild.
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***Data sharing statement*:** All data sets generated for this study are included in the manuscript.

***Ethics considerations*:** This study was approved by the University Cancer Center Frankfurt review board and the ethics committee at University Hospital Frankfurt. All patients included in our study gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2024.02.007.

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