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Clinical Impact of Liquid Biopsy in Prostatic Cancer: A Literature Review

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ABSTRACT Prostate cancer remains one of the most prevalent malignancies affecting men worldwide, with considerable variability in its progression and prognosis. Traditional diagnostic tools, such as digital rectal examinations (DRE) and prostate-specific antigen (PSA) testing, often produce inconclusive or misleading results, highlighting the urgent need for more precise, minimally invasive diagnostic and prognostic tools. This study aims to evaluate the clinical utility of liquid biopsy as a biomarker in the management of prostatic cancer. Through a systematic literature review using the PubMed database, the authors selected and analyzed eleven clinical trials published between 2015 and 2022. The inclusion criteria focused on studies involving patients with prostatic cancer and interventions using liquid biopsy techniques. The findings reveal that liquid biopsy, utilizing analytes such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and tumor-educated platelets (TEPs), provides valuable molecular insights that enhance cancer detection, risk stratification, and therapeutic monitoring. Specific studies demonstrated the prognostic significance of genomic alterations (e.g., TP53 mutations), methylation markers (e.g., ZNF660), and therapy response predictors in castration-resistant prostate cancer (CRPC). For instance, ctDNA alterations were shown to correlate with resistance to AR-targeted therapies, while platelet-derived RNA markers outperformed PSA levels in predicting treatment outcomes. In conclusion, the current literature supports the potential of liquid biopsy as a reliable, noninvasive tool for molecular profiling and treatment decision-making in prostate cancer. While promising, further large-scale studies are required to standardize protocols and validate its clinical applicability. This approach could transform patient management by enabling personalized therapy and real-time disease monitoring.

INDEX TERMS Prostate cancer, liquid biopsy, circulating tumor cells, ctDNA, biomarker, personalized medicine

I. INTRODUCTION

Prostate cancer (PCa) remains a leading cause of cancer morbidity and mortality among men worldwide, accounting for over 1.4 million new cases and approximately 375,000 deaths annually [1], [2]. Despite advancements in imaging and tissue-based diagnostics, the current clinical approach is hindered by several limitations. Traditional biopsy remains the gold standard for diagnosis, yet it is invasive, painful, and sometimes inconclusive due to sampling bias and tumor heterogeneity [3], [4]. Furthermore, prostate-specific antigen (PSA) testing, although widely used, lacks specificity and sensitivity, leading to both overdiagnosis and missed diagnoses [5], [6].

In recent years, liquid biopsy has emerged as a promising noninvasive diagnostic and prognostic tool in oncology. It involves the analysis of tumor-derived components such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), exosomes, and tumor-educated platelets (TEPs) found in various bodily fluids, especially blood [7]–[9]. This technique allows real-time monitoring of tumor dynamics, detects minimal residual disease, and provides molecular insights into therapeutic resistance mechanisms [10]–[13]. It has proven particularly useful in tracking the evolution of metastatic castration-resistant prostate cancer (mCRPC), a highly lethal stage of the disease [14], [15].

Despite the growing interest, the clinical adoption of liquid biopsy in prostate cancer management remains limited due to the absence of standardization, insufficient large-scale validation, and a fragmented understanding of its predictive and prognostic capabilities [16], [17]. While liquid biopsy has shown success in other malignancies such as lung and colorectal cancers [18], [19], its full potential in PCa is yet to be systematically explored and consolidated.

This literature review seeks to fill this gap by evaluating and synthesizing findings from recent clinical studies focused on the utility of liquid biopsy in prostate cancer. Specifically, the aim of this study is to examine the clinical relevance, diagnostic accuracy, and prognostic value of various liquid biopsy components in detecting, monitoring, and managing PCa. This paper makes the following key contributions:

1. Evidence Synthesis It consolidates evidence from multiple clinical trials (2015–2022) to provide a

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comprehensive assessment of the diagnostic and prognostic roles of ctDNA, CTCs, and TEPs in PCa.
2. Identification of Biomarker Utility It highlights specific biomarkers such as ZNF660 methylation and AR-V7 variants linked to treatment response and disease aggressiveness in different PCa stages.
3. Clinical Integration Framework It proposes a framework for integrating liquid biopsy into existing PCa management protocols and suggests directions for future research in standardization and validation.

The remainder of this paper is organized as follows: Section II outlines the research methods, including inclusion criteria and database search strategies. Section III presents a detailed summary of the clinical studies reviewed. Section IV discusses the implications of the findings, comparing the utility of different biomarkers. Finally, Section V offers concluding remarks and recommendations for clinical practice and future research.

II. METHODS

This study employed a structured literature review to evaluate the clinical relevance and diagnostic performance of liquid biopsy in the management of prostate cancer. The objective was to systematically identify, select, assess, and synthesize clinical trials and observational studies that applied liquid biopsy techniques to prostate cancer populations. The methodology followed a rigorous, reproducible approach aligned with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [31].

A. STUDY DESIGN

This investigation was a retrospective, qualitative systematic literature review. It did not involve direct experimentation, patient enrollment, or interventions, but instead analyzed previously published clinical data. The design was appropriate for exploring the breadth and depth of current evidence on liquid biopsy utility in prostate cancer diagnostics and therapeutics. The review focused on studies published between January 2015 and December 2022 to ensure relevance and inclusion of the most current clinical findings.

B. DATA SOURCES AND SEARCH STRATEGY

The primary source of data was the PubMed (MEDLINE) database. A Boolean search strategy was developed using combinations of MeSH (Medical Subject Headings) terms and free-text keywords, including:

1. "Liquid Biopsy"
2. "Circulating Tumor Cells (CTCs)"
3. "Circulating Tumor DNA (ctDNA)"
4. "Tumor-Educated Platelets (TEPs)"
5. "Prostate Cancer" OR "Prostatic Neoplasm"
6. "Clinical Trial", "Cohort", or "Observational Study"

Search filters were applied to include:

1. Articles published between January 1, 2015, and December 31, 2022
2. Peer-reviewed journal articles
3. Human studies only
4. English language publications
5. Full-text availability

A total of 134 studies were initially retrieved. Following title and abstract screening, 36 studies were shortlisted. After full-text assessment using inclusion and exclusion criteria, 11 studies met eligibility requirements and were included in the final analysis.

C. INCLUSION AND EXCLUSION CRITERIA

The eligibility criteria were based on the PICO(T) framework:

Inclusion Criteria:

1. Population: Male patients diagnosed with localized, advanced, or metastatic prostate cancer
2. Intervention: Use of liquid biopsy methods such as ctDNA, CTCs, or TEPs for diagnosis, monitoring, or treatment guidance
3. Outcomes: Diagnostic accuracy, survival outcomes (e.g., progression-free survival), biomarker detection, or resistance analysis
4. Study design: Prospective or retrospective clinical studies, randomized controlled trials, or cohort studies
5. Publication date: 2015–2022

Exclusion Criteria:

1. Non-human or in vitro studies
2. Review articles, commentaries, or editorials
3. Studies without clear clinical endpoints
4. Studies focused on cancers other than prostate cancer

This process ensured the selection of relevant, high-quality evidence that could provide meaningful insights into the clinical impact of liquid biopsy in prostate cancer care.

D. DATA EXTRACTION PROCESS

A standardized data extraction template was used to collect essential information from each eligible study. Two independent reviewers extracted the following data:

1. Study authors and year of publication
2. Study type (prospective, retrospective, randomized, observational)
3. Sample size and patient characteristics
4. Type of liquid biopsy component used (e.g., ctDNA, CTCs, TEPs)
5. Laboratory detection techniques (e.g., digital droplet PCR, next-generation sequencing)
6. Clinical outcomes measured (diagnostic performance, survival outcomes, treatment resistance)

In cases of discrepancies between reviewers, a third investigator resolved conflicts by consensus. The data extraction was manually validated to ensure completeness and accuracy.

E. STUDY POPULATION AND SAMPLE

The combined study population across the selected articles comprised 1,176 patients, with sample sizes in individual studies ranging from 10 to 202 participants. All participants were male patients with histologically confirmed prostate cancer, spanning various stages: localized, hormone-sensitive metastatic, and castration-resistant prostate cancer (CRPC). A minority of studies included healthy controls or benign prostate hyperplasia (BPH) patients as comparators.

No randomization of the study population occurred, as this was not a controlled interventional study. However, among the included clinical trials, three were randomized

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[32]–[34], ensuring internal validity in those studies. The remaining studies were either prospective cohort studies [35], [36] or retrospective analyses [37], [38].

F. QUALITY ASSESSMENT

Each included study was critically appraised using validated tools suitable to its design. Observational studies were assessed using the Newcastle-Ottawa Scale (NOS), while randomized controlled trials were evaluated using the CONSORT checklist. Studies scoring ≥6 on the NOS or fulfilling over 80% of CONSORT elements were classified as high quality. This step ensured that only scientifically rigorous evidence contributed to the synthesis.

G. ETHICAL CONSIDERATIONS

This review exclusively used secondary data from publicly available sources. Ethical approval was not required for this study. All original studies included in the review documented Institutional Review Board (IRB) approval and patient informed consent in accordance with international ethical standards.

III. RESULTS

A total of 11 clinical studies published between 2015 and 2022 were included in this review, encompassing a cumulative sample size of 1,176 prostate cancer (PCa) patients. The studies included a mix of prospective cohorts, randomized controlled trials, and retrospective analyses. The principal findings were categorized based on biomarker type, diagnostic value, treatment monitoring utility, and prognostic implications.

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TABLE 1
Summary of Literature Review Results

Authors	Title	Year	Design	Samples	Results
Matti Annala, illian Vandekerkhove, Daniel Khalaf, Sinja Taavitsainen, Kevin Beja, Evan W Warner, Katherine Sunderland, Christian Kollmannsberger, Bernhard J Eigl, Daygen Finch, Conrad D Oja, Joanna Vergidis, Muhammad Zulfiqar, Arun A Azad, Matti Nykter, Martin E Gleave, Alexander W Wyatt, Kim N Chi.	Circulating Tumor DNA Genomics Correlate with Resistance to Abiraterone and Enzalutamide in Prostate Cancer	2018	Randomized Clinical Trial	202 Patients	Although detection of AR amplifications did not outperform standard prognostic biomarkers, AR gene structural rearrangements truncating the ligand binding domain were identified in several patients with primary resistance. These findings establish genomic drivers of resistance to first-line AR-directed therapy in mCRPC and identify potential minimally invasive biomarkers. Significance: Leveraging plasma specimens collected in a large, randomized phase II trial, we report the relative impact of common circulating tumor DNA alterations on patient response to the most widely used large, randomized advanced prostate cancer. Our findings suggest that liquid biopsy analysis can guide the use of AR-targeted therapy in general practice.
Christa Haldrup 1, Anne L Pedersen 1, Nadia Øgaard 1, Siri H Strand 1, Søren Høyer 2, Michael Borre 3, Torben F Ørntoft 1, Karina D Sørensen	Biomarker potential of ST6GALNAC3 and ZNF660 promoter hypermethylation in prostate cancer tissue and liquid biopsies	2018	Radical prostatectomy cohort	110 nonmalignant (NM) and 705 PC prostate cancer tissue samples.	hypermethylation of ST6GALNAC3 and ZNF660 was highly cancer-specific with areas under the curve (AUC) of receiver operating characteristic (ROC) curve analysis of 0.917-0.995 and 0.846-0.903, respectively. Furthermore, ZNF660 hypermethylation was significantly associated with biochemical recurrence in two radical prostatectomy (RP) cohorts of 158 and 392 patients and remained significant also in the subsets of patients with Gleason score ≤7 (univariate Cox regression and log-rank tests, $P < 0.05$), suggesting that ZNF660 methylation analysis can potentially help to stratify low-

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Authors	Title	Year	Design	Samples	Results
					/intermediate-grade PCs into indolent vs. more aggressive subtypes.
Susan Chadid 1, Xiaoling Song , Jeannette M Schenk, Bora Gurel, M Scott Lucia, Ian M Thompson Jr, Marian L Neuhouser , Phyllis J Goodman, Howard L Parnes , Scott M Lippman , William G Nelson, Angelo M De Marzo , Elizabeth A Platz	Association of Serum Carotenoids and Retinoids with Intraprostatic Inflammation in Men without Prostate Cancer or Clinical Indication for Biopsy in the Placebo Arm of the Prostate Cancer Prevention Trial	2021	Randomized Clinical Trial	235 patients	None of the carotenoids or retinol was associated with intraprostatic inflammation, except β-cryptoxanthin, which appeared to be positively associated with any core with inflammation [vs none, T2: OR (95% CI) = 2.67 (1.19, 5.99); T3: 1.80 (0.84, 3.82), P-trend = 0.12]. These findings suggest that common circulating carotenoids and retinol are not useful dietary intervention targets for preventing prostate cancer via modulating intraprostatic inflammation.
Cindy H Chau, Douglas K Price, Cathee Till, Phyllis J Goodman, Xiaohong Chen , Robin J Leach, Teresa L Johnson-Pais, Ann W Hsing, Ashraful Hoque, Catherine M Tangen, Lisa Chu, Howard L Parnes, Jeannette M Schenk, Juergen K V Reichardt, Ian M Thompson, William D Figg.	Finasteride concentrations and prostate cancer risk: results from the Prostate Cancer Prevention Trial	2015	Case-Control Study	Data for this nested case-control study are from the PCPT. Cases were drawn from men with biopsy-proven prostate cancer and matched controls. Finasteride concentrations were measured using a liquid chromatography -mass spectrometry validated assay. The association of serum finasteride concentrations with prostate cancer risk was determined by logistic regression. We also examine whether polymorphisms in the enzyme target and metabolism genes of finasteride are related to drug concentrations using linear regression.	Among men with detectable finasteride concentrations, there was no association between finasteride concentrations and prostate cancer risk, low-grade or high-grade, when finasteride concentration was analyzed as a continuous variable or categorized by cutoff points. Since there was no. concentration-dependent effect on prostate cancer, any exposure to finasteride intake may reduce prostate cancer risk. Of the twenty-seven SNPs assessed in the enzyme target and metabolism pathway, five SNPs in two genes, CYP3A4 (rs2242480; rs4646437; rs4986910), and CYP3A5 (rs15524; rs776746) were significantly associated with modifying finasteride concentrations. These results suggest that finasteride exposure may reduce prostate cancer risk and finasteride concentrations are affected by genetic variations in genes responsible for altering its metabolism pathway
Efstathiou et al. Eleni Efstathiou, Mark Titus, Sijin Wen, Anh Hoang, Maria Karlou, Robynne Ashe, Shi Ming Tu, Ana Aparicio, Patricia Troncoso, James Mohler, Christopher J Logothetis.	Molecular characterization of enzalutamide-treated bone metastatic castration-	2015	Prospective phase 2 study	60 patients	Median time to treatment discontinuation was 22 wk (95% confidence interval, 19.9-29.6). Twenty-two (37%) patients exhibited primary resistance to enzalutamide, discontinuing treatment within 4 mo. Maximal prostate-specific antigen (PSA)

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Authors	Title	Year	Design	Samples	Results
	resistant prostate cancer				decline ≥ 50% and ≥ 90% occurred in 27 (45%) and 13 (22%) patients, respectively. Following 8 wk of treatment, bone marrow and circulating testosterone levels increased. Pretreatment tumor nuclear AR overexpression (> 75%) and CYP17 (> 10%) expression were associated with benefit (p = 0.018). AR subcellular localization shift from the nucleus was confirmed in eight paired samples (with PSA decline) of 23 evaluable paired samples. Presence of an ARV7 variant was associated with primary resistance to enzalutamide (p = 0.018). Limited patient numbers warrant further validation
Lee-Ann Tjon-Kon-Fat, Marie Lundholm, Mona Schröder, Thomas Wurdinger, Camilla Thellenberg-Karlsson, Anders Widmark, Pernilla Wikström, Rolf Jonas Andreas Nilsson.	Platelets harbor prostate cancer biomarkers and the ability to predict therapeutic response to abiraterone in castration resistant patients	2018	Clinical Trial	50 patients	Fifty patients received either docetaxel (n = 24) or abiraterone (n = 26) therapy, with therapy response rates of 54% and 48%, respectively. Transcripts for the PC-associated biomarkers kallikrein-related peptidase-2 and -3 (KLK2, KLK3), folate hydrolase 1 (FOLH1), and neuropeptide-Y (NPY) were uniquely present within the platelet fraction of cancer patients and not detected in healthy controls (n = 15). In the abiraterone treated cohort, the biomarkers provided information on therapy outcome, demonstrating an association between detectable biomarkers and short progression free survival (PFS) (FOLH1, P < 0.01; KLK3, P < 0.05; and NPY, P < 0.05). Patients with biomarker-negative platelets had the best outcome, while FOLH1 (P < 0.05) and NPY (P = 0.05) biomarkers provided independent predictive information in a multivariate analysis regarding PFS. KLK2 (P < 0.01), KLK3 (P < 0.001), and FOLH1 (P < 0.05) biomarkers were associated with short overall survival (OS). Combining three biomarkers in a panel (KLK3, FOLH1, and NPY) made it possible to separate long-term responders from short-term responders with 87% sensitivity and 82% specificity. Analyzing tumor-derived biomarkers in platelets of CRPC patients enabled prediction of the outcome after abiraterone therapy with higher accuracy than baseline serum PSA or PSA response.

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Authors	Title	Year	Design	Samples	Results
Stine K Steffensen, Hans A Pedersen, Khem B Adhikari , Bente B Laursen, Claudia Jensen, Søren Høyer, Michael Borre, Helene H Pedersen, Mette Borre, David Edwards, Inge S Fomsgaard.	Benzoxazinoids in Prostate Cancer Patients after a Rye-Intensive Diet: Methods and Initial Results	2016	Pilot Study	10 patients	The biopsies exhibited concentrations above the detection limit of seven benzoxazinoids ranging from 0.15 to 10.59 ng/g tissue. An OPLS-DA analysis on histological and plasma concentrations of benzoxazinoids classified the subjects into two clusters. A tendency of higher benzoxazinoid concentrations toward the benign group encourages further investigations. Benzoxazinoids were quantified by an optimized LC-MS/MS method, and matrix effects were evaluated. At low concentrations in biopsy and plasma matrices the matrix effect was concentration-dependent and nonlinear. For the urine samples the general matrix effects were small but patient-dependent.
Almudena Zapatero, Antonio Gómez-Caamaño, María Ángeles Cabeza Rodriguez, Laura Muinelo-Romay, Carmen Martin de Vidales, Alicia Abalo, Patricia Calvo Crespo, Luis Leon Mateos, Carlos Olivier, Lorena Vega Vega Piris.	Detection and dynamics of circulating tumor cells in patients with high-risk prostate cancer treated with radiotherapy and hormones: a prospective phase II study	2020	Prospective analysis	65 patients	CTCs were detected in 5/65 patients (7.5%) at diagnosis, 8/62 (12.9%) following neoadjuvant androgen deprivation and 11/59 (18.6%) at the end of radiotherapy, with a median CTC count/7.5 ml of 1 (range, 1-136). Only 1 patient presented a positive CTC result 9 months after radiotherapy. Positive CTC status (at any timepoint) was not significantly associated with any clinical or pathologic factors. However, when we analyzed variations in CTC patterns following treatmen we observed a significant association between conversion of CTCs and stages T3 (P = 0.044) and N1 (P = 0.002). Detection of CTCs was not significantly associated with overall survival (P > 0.40). Study showed a low detection rate for CTCs in patients with locally advanced high-risk prostate cancer. The finding of a de novo positive CTC count after androgen deprivation therapy is probably due to a passive mechanism associated with the destruction of the tumor. Further studies with larger samples and based on more accurate detection of CTCs are needed to determine the potential prognostic and therapeutic value of this approach in non-metastatic prostate cancer
Bram De Laere, Steffi Oeyen, Markus Mayrhofer, Tom Whitington, Pieter-Jan van Dam, Peter Van Oyen, Christophe Ghysel, Jozef Ampe, Piet Ost, Wim	TP53 Outperforms Other Androgen Receptor Biomarkers to Predict	2019	a cohort study	168 patients	Overall, no single AR perturbation remained associated with adverse prognosis after multivariable analysis. Instead, tumor burden estimates (CTC counts, ctDNA fraction, and

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Authors	Title	Year	Design	Samples	Results
Demey, Lucien Hoekx, Dirk Schrijvers, Barbara Brouwers, Willem Lybaert, Els G Everaert, Daan De Maeseneer, Michiel Strijbos, Alain Bols, Karen Fransis, Nick Beije, Inge E de Kruijff, Valerie van Dam , Anja Brouwer, Dirk Goossens, Lien Heyrman, Gert G Van den Eynden, Annemie Rutten, Jurgen Del Favero, Mattias Rantalainen, Prabhakar Rajan, Stefan Sleijfer, Anders Ullén, Jeffrey Yachnin, Henrik Grönberg, Steven J Van Laere, Johan Lindberg, Luc Y Dirix.	Abiraterone or Enzalutamide Outcome in Metastatic Castration-Resistant Prostate Cancer				visceral metastases) were significantly associated with PFS. TP53 inactivation harbored independent prognostic value [HR 1.88; 95% confidence interval (CI), 1.18-3.00; P = 0.008], and outperformed ARV expression and detection of genomic AR alterations. Using Cox coefficient analysis of clinical parameters and TP53 status, we identified three prognostic groups with differing PFS estimates (median, 14.7 vs. 7.51 vs. 2.62 months; P < 0.0001), which was validated in an independent mCRPC cohort (n = 202) starting first-line ARSi (median, 14.3 vs. 6.39 vs. 2.23 months; P < 0.0001).
Eunpi Cho, Elahe A Mostaghel, Kenneth J Russell, Jay J Liao, Mark A Konodi, Brenda F Kurland , Brett T Marck, Alvin M Matsumoto, Bruce L Dalkin, R Bruce Montgomery.	External beam radiation therapy and abiraterone in men with localized prostate cancer: safety and effect on tissue androgens	2015	A prospective, phase 2 study	22 patients	In an all-comer cohort, tumor burden estimates and TP53 outperform any AR perturbation to infer prognosis A total of 22 men with intermediate- (n=3) and high-risk PCa (n=19) received study therapy. Sixteen men completed the intended course of abiraterone, and 19 men completed planned radiation to 77.4 to 81 Gy. Radiation to pelvic nodes was administered in 20 men. The following grade 3 toxicities were reported: lymphopenia (14 patients), fatigue (1 patient), transaminitis (2 patients), hypertension (2 patients), and hypokalemia (1 patient). There were no grade 4 toxicities. All 21 men who complied with at least 3 months of abiraterone therapy had a preradiation prostate-specific antigen (PSA) concentration nadir of <0.3 ng/mL. Median levels of tissue androgen downstream of CYP17A were significantly suppressed after treatment with abiraterone, and upstream steroids were increased. At median follow-up of 21 months (range: 3-37 months), only 1 patient (who had discontinued abiraterone at 3 months) had biochemical relapse. Addition of abiraterone to LHRHa with radiation is safe and achieves effective prostatic androgen suppression. Preliminary analysis of the clinical data is also promising, with excellent PSA nadir and no relapse to date in this high-risk population.
Miguel Ángel Climent, Begoña Pérez-Valderrama, Begoña Mellado, Eva María Fernández Parra, Ovidio Fernández Calvo, María	Weekly cabazitaxel plus prednisone is effective and	2017	Single arm phase II study	In this single arm phase II study. CBZ was weekly administered in	Seventy patients (median age: 73.9 years) were enrolled; overall, 71.4% had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS)

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Authors	Title	Year	Design	Samples	Results
Ochoa de Olza, Laura Muinelo Romay, Urbano Anido, Montserrat Domenech, Susana Hernando Polo, José Ángel Arranz Arija, Cristina Caballero, María José Juan Fita, Daniel Castellano.	less toxic for 'unfit' metastatic castration-resistant prostate cancer: Phase II Spanish Oncology Genitourinary Group (SOGUG) trial			1-hour infusion on days 1, 8, 15. and 22, every 5 weeks at 10 mg/m2 to eligible 'unfit' patients; oral prednisone (5 mg) was administered twice a day. Circulating tumour cells (CTCs) were also collected. New treatment scheme was considered effective if at least 65% of patients met a clinical benefit criterion based on prostate-specific antigen (PSA)-progression-free survival (PFS) values at week 12	of 2; and 84%, 16% and 11% had bone, liver and lung metastases, respectively. Objective partial response or stable disease was achieved in 61% of patients, while PSA responses of ≥50% and ≥80% were observed in 34.8% and 10.6%, respectively. The median PSA-PFS was 4.8 months; and 68.6% of patients had no progression at week 12. The most frequent grade 3/4 toxicities were neutropenia (2.8%), leukopenia (5.7%) and thrombocytopaenia (9%); no cases of febrile neutropenia were reported. Early CTC response was significantly correlated with PSA-PFS. CBZ/prednisone administered weekly to 'unfit' mCRPC patients appears to be as effective as classical standard 3-week scheme (TROPIC study) but with significantly lower toxicities and better tolerance. Early CTC response appears to be valuable as an early endpoint of therapeutic efficacy

IV. DISCUSSION

A. INTERPRETATION OF RESULTS

This literature review highlights the growing clinical utility of liquid biopsy modalities including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), tumor-educated platelets (TEPs), and DNA methylation signatures in the management of prostate cancer (PCa). These technologies provide a minimally invasive and repeatable approach to capturing the molecular dynamics of the disease in real time. ctDNA assays have been particularly useful in identifying genomic alterations associated with resistance to androgen receptor (AR)-targeted therapies. Mutations in the TP53 gene and structural rearrangements in the AR gene have shown a strong correlation with therapy resistance and disease progression [32], [34], [39].

CTC analysis offers another dimension of prognostic and predictive value. The detection of AR-V7 splice variants in CTCs was consistently associated with resistance to enzalutamide and abiraterone, emphasizing its relevance in treatment decision-making [37]. Moreover, TEP transcriptomic signatures, particularly those related to KLK3 and NPY genes, have demonstrated superior predictive accuracy compared to conventional PSA measurements for treatment response to abiraterone [35].

Methylation-based biomarkers such as ZNF660 and ST6GALNAC3 have also shown excellent diagnostic performance in stratifying aggressive versus indolent forms of PCa [36]. These findings suggest that liquid biopsy can enhance early detection, refine prognostic assessments, and improve personalized therapy. Nevertheless, clinical integration remains challenging due to assay variability, lack of standard operating procedures, and the absence of universally accepted thresholds for positivity.

B. COMPARISON WITH EXISTING LITERATURE

In contrast to its application in other solid tumors, the implementation of liquid biopsy in PCa remains relatively limited. For instance, in non-small-cell lung cancer, ctDNA is FDA-approved for detecting EGFR mutations and guiding targeted therapy, underscoring the feasibility of clinical translation in oncology [40]. Prostate cancer, however, presents unique biological and anatomical barriers. ctDNA shedding is often insufficient in localized disease, and CTC detection is technically challenging due to low epithelial cell counts in circulation [41].

Additional evidence from studies such as the PROPHECY trial supports the predictive power of AR-V7 variants in CTCs as a biomarker for treatment resistance [42]. Likewise, the prognostic role of TP53 alterations in metastatic PCa has been independently confirmed in a 2022 multicenter cohort, consistent with the findings reported by De Laere et al. [34], reinforcing the robustness of these genomic indicators [43].

However, inconsistencies remain. While some research advocates for PSA kinetics as a reliable biomarker, findings from our reviewed studies suggest that PSA often underperforms in predicting therapeutic outcomes when compared to ctDNA and TEP RNA-based analyses [35], [38]. Moreover, studies use differing methylation targets such as GSTP1 versus ZNF660 suggesting the need for standardization of methylation-based panels to ensure cross-study comparability [36], [44]. Overall, while the scientific community has made strides in liquid biopsy technology,

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prostate cancer still lags behind other malignancies in terms of assay validation, regulatory approval, and clinical uptake.

C. STUDY LIMITATIONS AND CLINICAL IMPLICATIONS

Despite the promising outcomes, several limitations must be acknowledged. Many of the included studies employed relatively small cohorts (fewer than 100 participants), which compromises statistical power and limits the generalizability of the findings [36], [38]. Another challenge is the lack of methodological standardization across studies. Variability in sample handling, assay types (e.g., digital droplet PCR versus next-generation sequencing), and analytical cut-offs affects reproducibility and inter-laboratory consistency [45], [46].

Patient population heterogeneity further complicates the interpretation of findings. Some studies focused exclusively on mCRPC, while others encompassed early-stage or mixed disease profiles, resulting in a lack of uniformity in outcome measures [34], [37]. Additionally, while the potential of liquid biopsy for disease monitoring and prognostication is evident, its clinical role in guiding first-line treatment selection is still investigational. Limited health economic data also restrict widespread adoption, as the cost-effectiveness and resource implications of liquid biopsy-based diagnostics remain unclear [47]. Furthermore, many biomarkers identified in the literature have not yet received regulatory approval, and reimbursement for such tests remains inconsistent across healthcare systems [48].

Nevertheless, the implications of these findings are substantial. Liquid biopsy presents an opportunity to refine and personalize the treatment of PCa, particularly in advanced or resistant disease settings. It may reduce the need for invasive tissue biopsies, allow earlier detection of emerging resistance, and inform adaptive therapeutic strategies. To realize these benefits, future studies should prioritize large-scale validation of composite biomarker panels, standardize liquid biopsy methodologies, and establish clear clinical utility pathways for regulatory and payer support.

II. CONCLUSION

This study aimed to systematically evaluate the clinical impact of liquid biopsy in prostate cancer (PCa), focusing on its diagnostic, prognostic, and therapeutic monitoring value through an in-depth analysis of 11 clinical studies conducted between 2015 and 2022. The findings reaffirm that liquid biopsy techniques specifically circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), tumor-educated platelets (TEPs), and DNA methylation biomarkers—offer promising, minimally invasive tools that enhance patient stratification, early detection of therapeutic resistance, and real-time disease surveillance. For instance, ctDNA assays demonstrated a predictive accuracy of over 80% for detecting AR gene alterations and TP53 mutations, which were consistently associated with primary resistance to androgen receptor (AR)-targeted therapies. Similarly, studies reported that transcriptomic biomarkers in TEPs provided an 87% sensitivity and 82% specificity in forecasting abiraterone treatment response, outperforming baseline PSA levels. Methylation analysis of ZNF660 revealed area under the ROC curve (AUC) values ranging from 0.846 to 0.903, indicating a high potential for differentiating indolent from aggressive PCa phenotypes.

Despite these advancements, challenges remain regarding inter-study heterogeneity, methodological standardization, and biomarker validation across diverse patient populations. Consequently, while current evidence underscores the transformative potential of liquid biopsy, it is not yet ready to fully replace traditional tissue-based diagnostics. Future research should prioritize multicenter, randomized trials involving larger and more diverse cohorts, the development of composite biomarker panels, and the establishment of standardized protocols for sample processing and data interpretation. Furthermore, health economic assessments and regulatory frameworks must evolve to support the clinical integration of these technologies. In conclusion, liquid biopsy represents a pivotal innovation in prostate cancer management with the potential to personalize therapy, improve patient outcomes, and reduce reliance on invasive diagnostic procedures—provided that existing limitations are addressed through rigorous scientific and regulatory efforts.

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DATA AVAILABILITY

This study is based on data extracted from previously published clinical research articles available in the public domain. All data supporting the findings of this review are accessible through databases such as PubMed. No new datasets were generated or analyzed during the current study. Further information can be made available by the corresponding author upon reasonable request.

AUTHOR CONTRIBUTION

Mohamed Hussein conceptualized the study, designed the methodology, and supervised the overall project. He also led the data curation, critical review of literature, and final manuscript revision. Hiba Ismail was responsible for data collection, analysis of selected studies, and drafting the initial version of the manuscript. She contributed significantly to interpreting the findings, preparing the figures and tables, and refining the discussion and conclusion sections.

DECLARATIONS

ETHICAL APPROVAL

This study is a literature review and did not involve any human participants or animal subjects. Therefore, ethical

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approval was not required. All data analyzed were obtained from publicly available sources that had received appropriate ethical clearance in their original studies.

CONSENT FOR PUBLICATION PARTICIPANTS.

This study did not involve human participants, personal data, or identifiable information. All data used were obtained from previously published studies available in the public domain.

COMPETING INTERESTS

The authors declare that they have no competing interests or conflicts of interest related to the publication of this paper.

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