Circulating biomarkers and treatment response

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Prostate Cancer Biomarkers working group

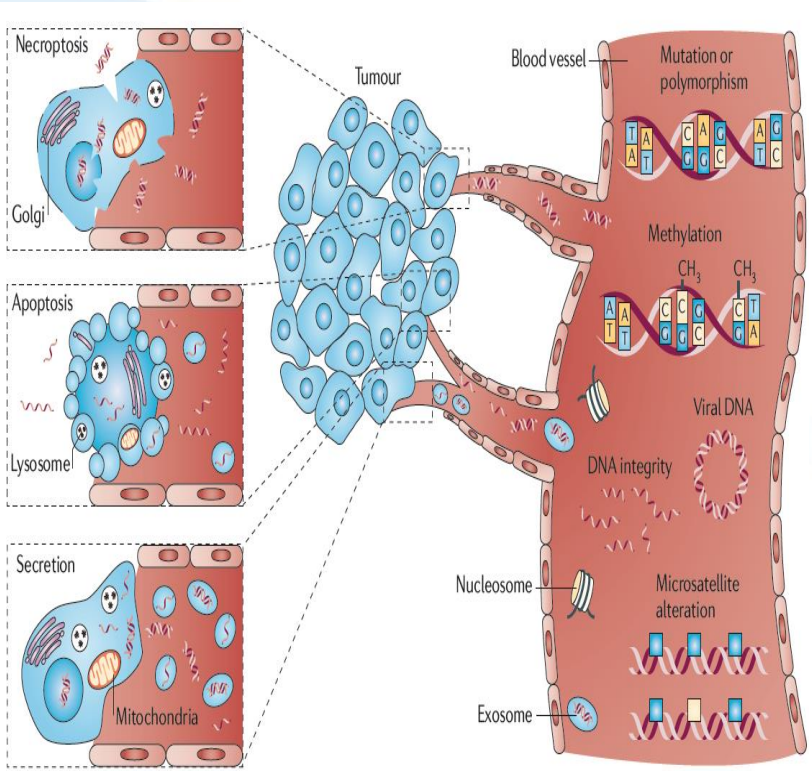
Evaluation of Level of Evidence (LOE) for tumor markers in PCa

WP1 : LOE for biomarkers at time of diagnostics[1]

WP2 : LOE for prognostic biomarkers used for localized prostate cancer management[2]

WP3 : LOE for circulating predictive biomarkers for mPC[3]

1: Lamy PJ Ann Bio Clin 2016 ; 2: Lamy PJ Eur Urol Focus 2018 ; 3: Badoudjian M Eur Urol Oncol 2024



From Schwartzenbach Nat Rev Cancer2011

Context

Metastatic prostate cancer (mPCa) harbors genomic/proteic alterations that may predict targeted therapy efficacy.

These alterations can be identified in tissue but also directly in **biologic fluids (i.e. liquid biopsies), mainly blood**.

Liquid biopsies may represent a safer and less invasive and sometimes the only alternative for monitoring patients treated for mPCa.

WP3 Objective:

Systematically review the current level of evidence[1] on liquid biopsy biomarkers for predicting treatment response in mPCa.

Elements of tumor marker studies that constitute Levels of Evidence determination[1]

LEVEL OF EVIDENCE	DESCRIPTION OF THE STUDIES	VALIDATION STUDIES MANDATORY
LOE IA	Prospective RCT	Not required
LOE IB	Prospective studies using prospectively archived samples	1 or 2 studies with concordant results
LOE IIB	Prospective studies using prospectively archived samples	No studies or several studies with inconsistent results
LOE IIC	Prospective-observational (register)	1 or 2 studies with concordant results
LOE IIIC	Prospective-observational (register)	No studies or 1 study with concordant or non-concordant results
LOE IV-VD	Retrospective-observational	

1:adapted from Simon RM JNCI 2009 Nov 4;101(21):1446–1452.

Attribution of LOE IB: Prospective studies using prospectively archived samples

1) The results must be confirmed in at least one other study similar to the previous one

2) The samples available must be representative of the trial population (at least 2/3) selected in such a way to avoid selection bias.

3) Pre-analytical data must be perfectly controlled/ the test must be pre-analytically and analytically validated

4) The study design should be completely defined and written before conducting testing

5) The study design and analysis must investigate the utility of the marker for specific clinical use.

6) The clinical data (judgment criteria and treatment) must be blinded.

Otherwise the study is downgraded

Evidence acquisition

-Publications on circulating biomarkers in mPCa, indexed in Medline®, Web of Science™ or evidence-based websites between **March 2013 and February 2024**, were systematically searched and reviewed.

-Endpoints were: prediction of overall survival, biochemical or radiographic progression-free survival after treatment [i.e. chemotherapy, androgen deprivation therapy, androgen receptor pathway inhibitors (ARPi), immunotherapy or poly(ADP-ribose) polymerase inhibitors (PARPi)].

The study focused on the **PICOS criteria**:

1) **P**opulation: patients with mPCa, mHSPC or mCRPC, or NEPC;

2) **I**ntervention : assessed liquid biomarkers

3) **C**ompared intervention : other clinical or biological parameters

4) **O**utcome : biomarker predictive value for treatment efficacy [overall survival (OS) or biochemical/radiographic progression-free survival (PFS)] of chemotherapy, androgen deprivation therapy (ADT), androgen receptor pathway inhibitors (ARPi), immunotherapy or PARPi;

5) **S**tudy design (S): meta-analysis, randomized controlled trial, prospective non-randomized study, or retrospective study

Exclusion criteria

Publications deemed ineligible were:

i) health economic studies

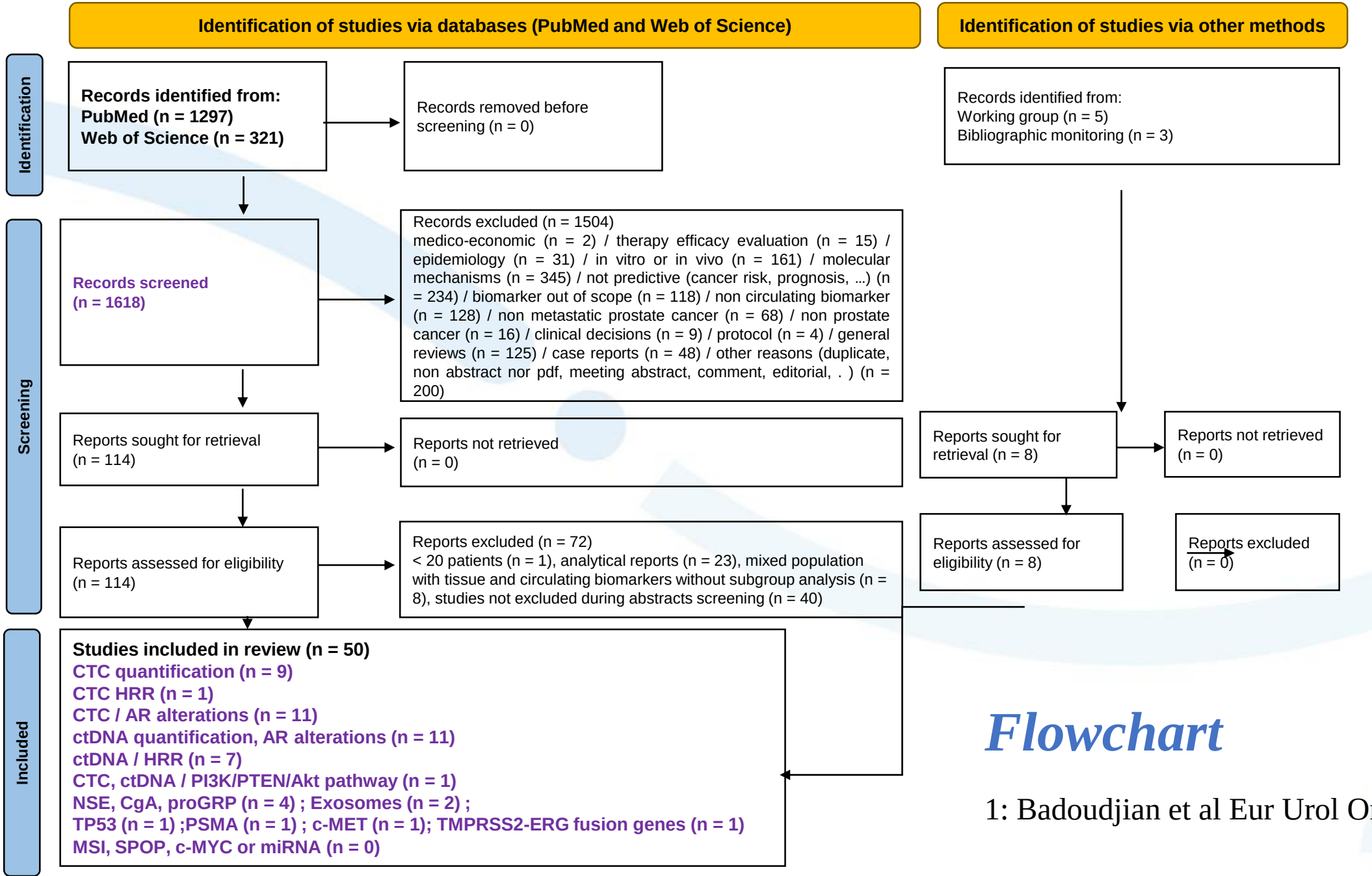
ii) studies on the impact of tests on clinical decision-making (practice surveys)

iii) studies on salivary tests

iv) studies exclusively based on germline biomarkers

v) studies performed using both tissue and circulating biomarkers without subgroup analysis

vi) studies involving ≤20 patients



Flowchart

1: Badoudjian et al Eur Urol Oncol 2024

CTCs: detection/quantification

- All studies (1-12) on patients with mCRPC showed that CTC detection (threshold related to the technique used) before treatment was associated with poorer PFS or OS after
treatment (ARPi, docetaxel, radium)

- Limitations: Lack of comparator (negative biomarker population without CTC detection) and the absence in some studies of biomarker measurement before treatment initiation (baseline) (2,4,5,7,8,9)

- 3 studies (10,11,12) showed predictive value of cabazitaxel, abiraterone and radium-233, respectively with (LOEIIB)

1 Davies CR, Frontiers in oncology. 2023;12. 2 Di Lorenzo G, Clinical genitourinary cancer. 2021;19:e286-e98. 3 Goldkorn A, Clinical Cancer Research. 2021;27:1967-73. 4 Miyamoto DT,. Cancer discovery. 2018;8:288-303. 5 Caries J, Clinical genitourinary cancer. 2018;16:E1133-E9. 6 Thalgott M, Journal of cancer research and clinical oncology. 2015;141:1457-64. 7 Thalgott M, BMC cancer. 2015;15. 8 Okegawa T, Anticancer research. 2014;34:6705-10.9 Goodman OB, Clinical genitourinary cancer. 2011;9:31-8. 10 de Jong AC JCO precision oncology. 2023;7:e2300156. 11 Koinis F, Cancers (Basel). 2023;15. 12 Gu T International urology and nephrology. 2023;55:883-92.

CTCs: AR mutations/amplification/splice variants

Twelve studies were identified (1-12)

The presence of AR splice variant 7 (AR-V7) transcripts or the AR-V7 protein level in CTCs was associated with ARPi resistance (shorter PFS and OS) [3] [5] [8] [11] (LOE IB) and also with shorter OS after taxane chemotherapy [6] [9-10] (LOE IB).

1 Hirano H, Scientific reports. 2023;13. 2 Stuopelyte K, The Journal of urology. 2020;204:71-8. 3 Erb HHH, Urologia internationalis. 2020;104:253-62.4 Taplin ME, European urology. 2019;76:843-51. 5 Okegawa T, The Prostate. 2018;78:576-82. 6 Scher HI, JAMA oncology. 2018;4:1179-86. 7 To SQ, Prostate Cancer. European urology. 2018;73:818-21.8 Antonarakis ES, Journal of clinical oncology 2017;35:2149-56. 9 Antonarakis ES, JAMA oncology. 2015;1:582-91. 10 Scher HI, JAMA oncology. 2016;2:1441-9. 11 Antonarakis ES, The New England journal of medicine. 2014; 12 Sepe P, Ther Adv Med Oncol 2024;16:17588359231217958

ctDNA: detection/quantification/alterations in genes not related to HRR or AR

Fourteen studies were identified

Risk scores that combine several gene alterations appeared to have a better predictive value than individual gene alterations (e.g., *AR* amplification alone) or clinical risk factors in predicting primary resistance and time to progression in patients with mCRPC treated with abiraterone [1-4] (LOE IB).

1 Xia S, Oncotarget. 2015;6:16411-21. 2 Xia Y, Oncotarget. 2016;7:35818-31. 3 Du M, Prostate cancer and prostatic diseases. 2020;23:705-13.4 Huang JY, Cancers. 2022;14.

ctDNA: abnormalities in HRR genes

Nine studies were identified

(1) High detection concordance between liquid biopsy (ctDNA) and tissue samples (80–90%) for these HRR pathway gene alterations, particularly for BRCA1,2/ATM [1-4] (LOE IB)

(2) Prediction of PARPI response in patients with HRR gene alterations detected in liquid biopsies (ctDNA) [5-9] (LOEI B)

Note that BRCA2 was the most frequent alteration relative to PARPi efficacy

1 Matsubara N, Clin Cancer Res 2023;29:92-9.2 Chi KN, Clin Cancer Res 2023;29:81-91. 3 Tukachinsky H, Clin Cancer Res 2021;27:3094-105. 4 Yang B, iScience 2024;27:108931. 5 Fizazi K, Nat Med 2024;30:257-64. 6 Fizazi K, N Engl J Med 2023;388:719-32. 7 Zhu H, Heliyon 2023;9: e13827. 8 Clarke NW, NEJM Evid 2022;1:EVIDoa2200043. 9 Chi KN, Clin Oncol 2023;41:3339-51

ctDNA: AR mutations or amplification

Ten studies were identified

Studies on the predictive value of AR amplifications or mutations for ARPI response were concordant [1-3]: shorter clinical or radiographic PFS was associated with the presence of AR alterations [1,3] (LOE IIB).

For patients with harboring wild-type TP53 and previously treated with chemotherapy and an ARPI, accumulation of AR alterations (variants, amplification, gene rearrangement) had an additive effect on the risk of progression during second-line ARPI therapy [4] (LOE IIB).

1 Wyatt AW, JAMA Oncol 2016;2:1598-606; 2 Dong B, J Natl Compr Cancer Netw 2021;19:905-14. 3 Annala M, Cancer Discov 2018;8:444-57 ; 4 De Laere B, JAMA Oncol 2019;5:1060-2

Circulating neuroendocrine markers

Four studies were identified [1-4]

A meta-analysis (4) of six studies involving 353 patients with mCRPC suggested that circulating neuroendocrine markers (elevated CgA or CgA + NSE) were associated with shorter OS (HR 3.838, 95% CI 1.774–8.304; p = 0.001) after ARPI treatment.

Globally, LOE do not reached sufficient level for the use in clinics (Max LOEIII C)

1 Yashi M, Cancer Rep 2023;6:e1762. 2 Derlin T ? J Nucl Med 2020;61:1602-6. 3 Rathke H, J Nucl Med 2020;61:689-95. 4 Liu Y, Zhao S, Wang J, et al. Urol Int 2019;102:373-84

Other circulating biomarkers

Two studies on exosomes were identified [1,2
Exosomal TUBB3 mRNA (coding for beta-tubulin III) predicted shorter biochemical PFS after abiraterone treatment (1)

Exosomal AKR1C3 mRNA (catalyze the conversion of aldehydes and ketones to their corresponding alcohols/role in cell growth & differentiation) predicted PFS (3.9 vs 10.1 mo; HR 3.81, 95% CI 1.69–8.58; p = 0.001) and OS (16.2 vs 32.5 mo; HR 5.41, 95% CI 2.44–12.01; p < 0.001) under abiraterone therapy (2)

LOEIIB

1 Zhu S, Cancer Med. 2021 Sep;10(18):6282-6290. 2 Zhu S, Oncologist. 2022 Nov 3;27(11):e870-e877.

CONCLUSIONS

Several biomarkers with a high LOE (IB) are useful alternatives to tissue sample analyses for predicting response to treatment in patients with mPCa.

-CTC quantification (cabazitaxel, abiraterone and radium-233) and CTC AR-V7 (ARPi)

-ctDNA quantification/alteration (non HRR Non AR) abiraterone

-BRCA mutation (HHR genes) detection in ctDNA (PARPi)

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THANK YOU FOR YOUR ATTENTION

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