SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

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FAZEKAS TAMÁS

Urológia

című program

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Prostate Cancer Screening, Molecular Diagnostics, and Therapy Prediction: Toward Personalized Care

Ph.D. Thesis

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"Start by doing what is necessary, then what is possible,

and suddenly you are doing the impossible."

Saint Francis of Assisi

TABLE OF CONTENS

1. List of abbreviations

PCa – Prostate Cancer

PSA – Prostate-Specific Antigen

PCSM – Prostate Cancer-Specific Mortality

OS – Overall Survival

EAU – European Association of Urology

NCCN – National Comprehensive Cancer Network

MRI – Magnetic Resonance Imaging

HRR – Homologous Recombination Repair

BRCA – Breast Cancer Gene (1 and 2)

PARP – Poly (ADP-ribose) Polymerase

PARPi – PARP Inhibitor

mCRPC – Metastatic Castration-Resistant Prostate Cancer

ADT – Androgen Deprivation Therapy

ARPI – Androgen Receptor Pathway Inhibitor

PSMA – Prostate-Specific Membrane Antigen

PI-RADS – Prostate Imaging Reporting and Data System

ISUP – International Society of Urological Pathology

CDR – Cancer Detection Rate

PPV – Positive Predictive Value

OR – Odds Ratio

CI – Confidence Interval

RoB – Risk of Bias

RCT – Randomized Controlled Trial

PROSPERO – International Prospective Register of Systematic Reviews

CoCoPop – Condition-Context-Population

PICO – Population-Intervention-Comparison-Outcome

PSA50 – ≥50% PSA Decline

PFS – Progression-Free Survival

IPD – Individual Patient Data

bpMRI – Biparametric MRI

mpMRI – Multiparametric MRI

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

ctDNA – Circulating Tumor DNA

Lu-PSMA – Lutetium-labeled PSMA

Ac-PSMA – Actinium-labeled PSMA

2. Student profile

2.1. Vision and mission statement, specific goals

My vision is that precision medicine and individualized molecular targeted therapy, is going to revolutionize oncology care with improving outcomes and quality of life. In line with this, my specific mission is to identify predictive biomarkers that guide optimal therapy sequencing in prostate cancer, driving personalized treatment approaches and advancing clinical decision-making. My specific goals were to assess the treatment sensitivity of prostate cancer patients with *BRCA* mutations, and to assess the role of MRI in prostate cancer screening.

2.2. Scientometrics

Number of all publications:	
Cumulative IF:	186.53
Av IF/publication:	3.66
Ranking (SCImago):	D1: 17, Q1: 16, Q2: 10, Q3: 1, Q4: 2
Number of publications related to the subject of the thesis:	3
Cumulative IF:	34.5
Av IF/publication:	12.2
Ranking (SCIMago):	D1: 3, Q1: 0, Q2: 0
Number of citations on Google Scholar:	333
Number of citations on MTMT (independent):	143
H-index:	6

2.3. Future Plans

My primary focus will be on launching prospective studies and clinical trials to optimize personalized care for patients with prostate cancer. Moreover, I aim to enhance the global visibility and impact of both my department and our research by creating stronger international collaborations and actively participating in major urological and oncological research networks.

3. Summary of the PhD

Prostate cancer is one of the most prevalent malignancies in men, with a compelling need for improved early detection and individualized treatment strategies. PSA-based screening, while effective in reducing cancer-specific mortality, often results in overdiagnosis and unnecessary biopsies. Simultaneously, *BRCA* mutations have emerged as key biomarkers in predicting prognosis and treatment response in metastatic castration-resistant prostate cancer. Therefore, utilizing systematic reviews and meta-analyses, we aimed to evaluate the performance of MRI-based screening strategies versus PSA-only approaches in population-based PCa screening (Project I) and to assess the efficacy of standard (abiraterone, enzalutamide, docetaxel) and later-line therapies (PARP inhibitors, platinum-based chemotherapy, PSMA-ligands, cabazitaxel) in *BRCA*-positive metastatic castration-resistant prostate cancer patients (Project II).

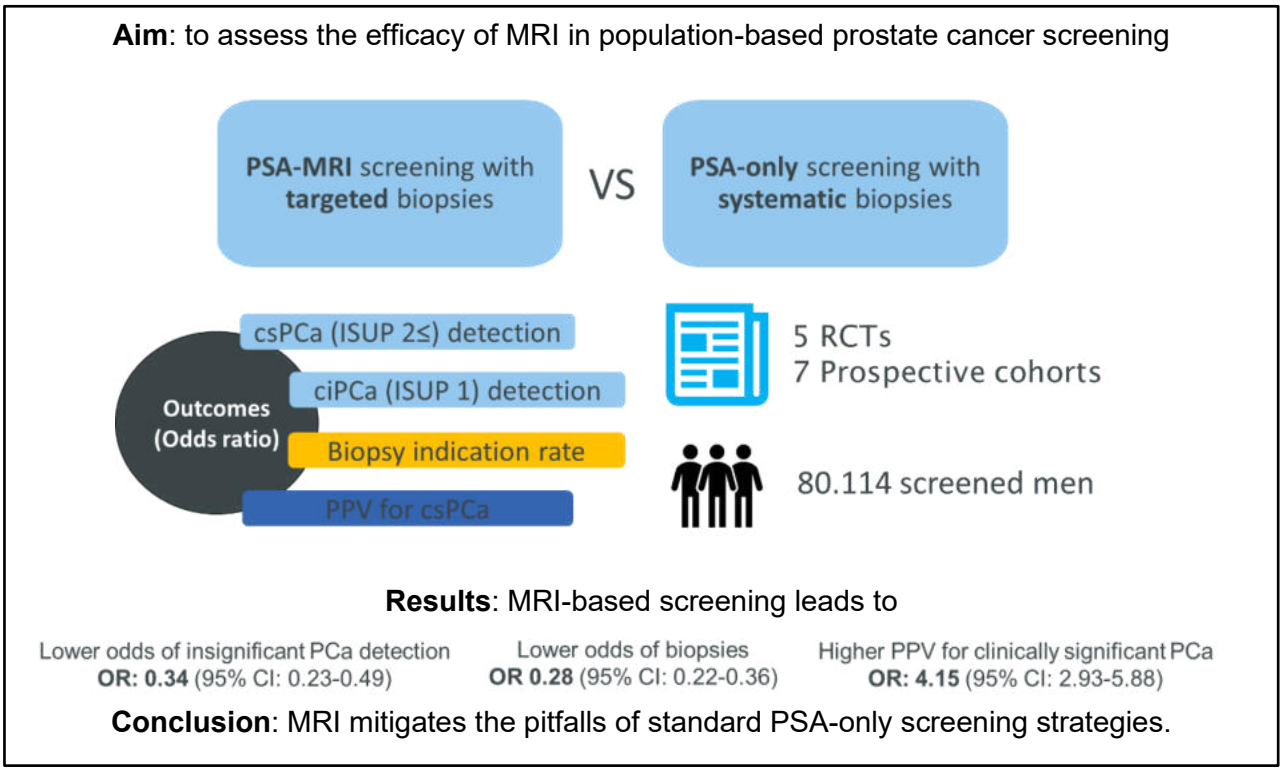
In our 1st project, we found that MRI, particularly when used as a reflex test after PSA, significantly reduced the detection of clinically insignificant prostate cancer and the number of biopsies, without compromising the detection of significant cancers. Moreover, biparametric MRI and higher PI-RADS thresholds (≥4) enhanced positive predictive value and minimized unnecessary interventions.

In our 2nd project, we showed that standard therapies are effective in *BRCA*-positive metastatic castration-resistant prostate cancer patients, with enzalutamide showing superior PSA response and progression-free survival. Furthermore, PARP inhibitors demonstrated consistent efficacy across different compounds. Interestingly, platinum-based chemotherapy provided similar outcomes to PARPi, supporting its role in *BRCA*-mutated metastatic castration-resistant prostate cancer.

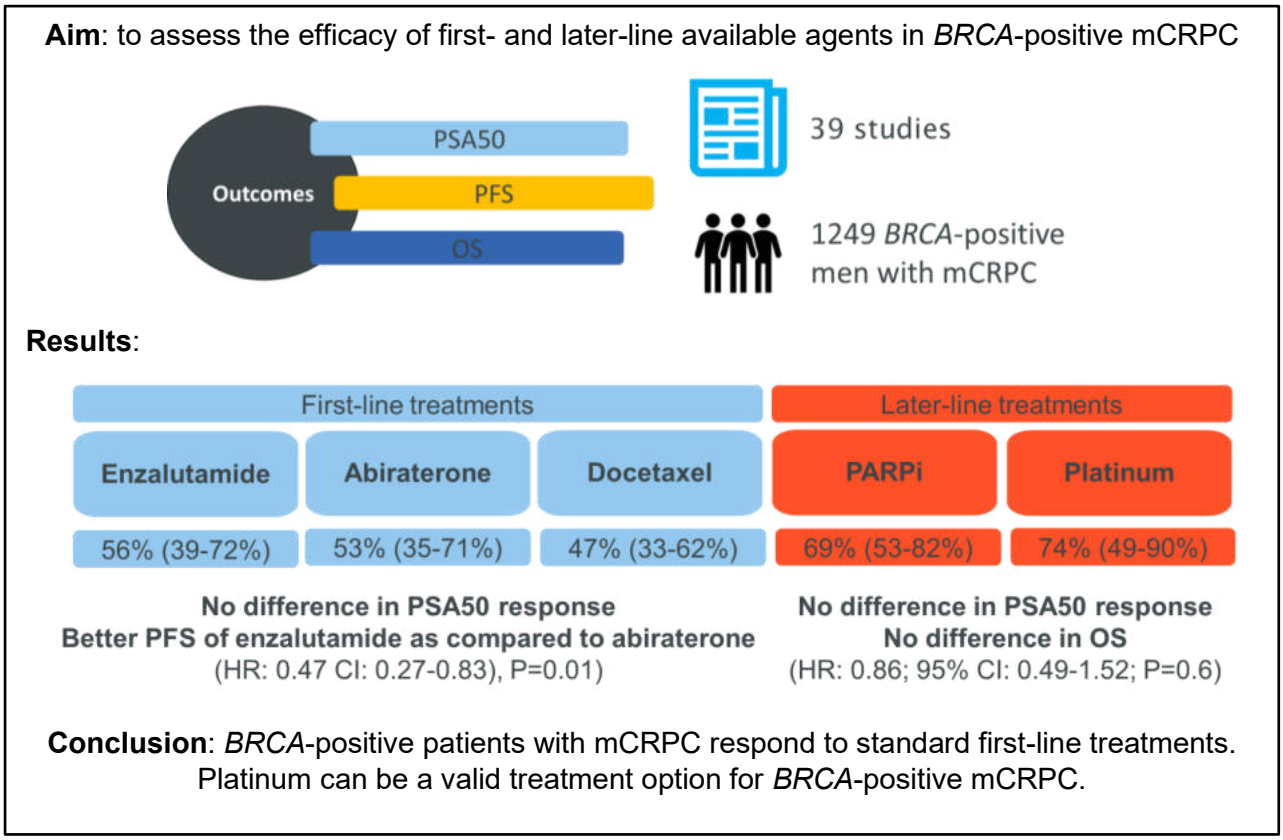
We concluded that the application of MRI in PSA positive cases can optimize early detection, while reducing overtreatment in prostate cancer screening. For *BRCA*-positive metastatic castration-resistant prostate cancer patients, standard and targeted therapies show meaningful efficacy, with platinum-based chemotherapy emerging as a viable alternative to PARPi. These findings support more personalized and biomarker-driven approaches in both prostate cancer screening and treatment, informing clinical practice guidelines.

4. Graphical abstract

4.1. Project I



4.2. Project II



5. Introduction

5.1. Prostate cancer as a major public health issue

Prostate cancer (PCa) is the second most common solid tumor in men after non-melanoma skin cancer, with more than one million new cases worldwide in 2020, an estimated incidence of 473,344 new cases per year in Europe, placing a significant burden on health care systems (1, 2). As a result of improvements in the treatment landscape and diagnostics, PCa mortality has been decreasing since the mid-1990s (3). Notably, the five-year relative survival of localized and locoregional disease is nearly 100%, however, it is only 32.3% for distant metastatic disease, with at the same time treatment costs exponentially rising with advanced disease stage, highlighting the need for improvement in early detection, diagnostics, and development of prognostic and predictive biomarkers to aid clinical decision-making (2, 3).

5.2. Early detection and screening of prostate cancer

Prostate-specific antigen (PSA)-based population-wide PCa screening reduces metastasis and PCa-specific mortality (PCSM), but at the same time leads to unnecessary biopsies, overdiagnosis of clinically insignificant disease, overtreatment a moderate reduction of PCSM and but an unclear impact on overall survival (OS) (4, 5). To balance the potential risks and benefits, current clinical practice guidelines, such as the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN), recommend informing patients about the advantages and pitfalls of PSA testing (6, 7). Through shared decision-making that considers individual factors such as family history, personal values, and priorities, clinicians can identify well-informed candidates most likely to benefit from early PCa detection (8). However, this opportunistic approach often varies in quality and has led to widespread but untargeted testing accompanied by disparities in health care access and literacy (8, 9). For example, in France and the United Kingdom, elderly men who are unlikely to benefit from PSA testing are more likely to undergo the test than men in their 50s (10, 11). Moreover, opportunistic screening has not been shown to improve PCSM, and the inherent limitations of PSA-based PCa screening have not been addressed (9, 12, 13).

Prostate magnetic resonance imaging (MRI) has been widely utilized as a clinical tool to enhance detection, and biopsy targeting of PCa lesions, particularly in patients with a

clinical suspicion of the disease (6, 14, 15). Pre-biopsy bi- or multiparametric MRI followed by cognitive or image-fusion targeted biopsies have been shown to improve diagnostic accuracy by improving the detection of clinically significant PCa, while reducing the number of unnecessary biopsies and insignificant cancers in a clinical setting (14-16). Consequently, EAU guidelines recommend pre-biopsy MRI, and targeted biopsy-only, however, there is no clear consensus on the integration of MRI in the PCa detection pathway in the screening setting (6). To address this gap, and to overcome the limitations of conventional PSA-based screening, several ongoing clinical trials are investigating the value of incorporating MRI and targeted biopsies into population-based PCa screening protocols. Therefore, in the setting of a large body of literature addressing the diagnostic role of prostate MRI and its growing global use, there is a need to synthesize evidence to inform clinical practice and help devise a screening strategy that incorporates MRI information.

5.3. Novel biomarkers of prostate cancer: the Breast Cancer Gene 1 and 2

One of the best-established prognostic and predictive biomarkers for PCa are the mutations in Breast Cancer Gene 1 or 2 (*BRCA*). Under physiological conditions, these genes and their protein products play a crucial role in the homologous recombination repair (HRR) of double-strand DNA breaks (17). While loss-of-function mutations in *BRCA* result in elevated mutation burden and accelerated tumorigenesis, leading to a more aggressive PCa with an earlier onset of disease, inferior prognosis, and unfavorable clinicopathological features (18-21). Beside their prognostic utility, these genes have been established as distinct targets for precision medicine. Inhibition of the base-excision repair enzymes poly (ADP-ribose) polymerase (PARP) 1 and 2 leads to tumor cell death, particularly in cells with deficiencies in DNA repair mechanisms – most notably the homologous recombination repair (HRR) pathway including *BRCA* (22). This phenomenon, known as 'synthetic lethality,' forms the basis of the antitumor activity of PARP inhibitors (PARPi) in patients with advanced PCa (22). Specifically, olaparib and rucaparib are approved as monotherapies, while combination therapies include olaparib with abiraterone, niraparib with abiraterone, and talazoparib with enzalutamide in patients with metastatic castration-resistant PCa (mCRPC) to date (23, 24). The combination of PARPi with ARPI is based on the hypothesized the proposed synergistic interaction between the two agents. Recent *in vivo* and *in vitro* studies have highlighted the interplay

between androgen receptor signaling and double-stranded DNA repair mechanisms (25-27). Androgen receptor activity has been shown to promote the non-homologous end-joining repair pathway, which, along with homologous recombination repair HRR, is responsible for repairing double strand DNA breaks (25-27). This crosstalk between the androgen receptor signaling and DNA repair has led to the hypothesis that ARPIs could induce synthetic lethality in HRR-deficient prostate cancers. In this context, ARPIs may amplify the impact of HRR defects, potentially enhancing therapeutic response to PARPi even in patients without HRR alterations. This mechanism raises the question of which standard treatment (ARPI) offers the greatest efficacy for mCRPC patients.

Besides PARPi, platinum-based chemotherapy can exploit defects in DNA-repair genes as well, therefore can be offered for patients with mCRPC and HRR mutations after progression on standard treatments (23).

According to the literature, *BRCA* mutations (both germline and somatic) occur in approximately 1-2% of patients with PCa, and around 4-13% in patients with advanced disease, with *BRCA2* being more common than *BRCA1*, and somatic being more frequent than germline mutations (21, 28-31). Considering the robust clinical implications of *BRCA* mutations, clinical practice guidelines recommend genetic testing for PCa patients with positive family history, high-risk or very high-risk localized or metastatic disease (6, 7, 23). With the growing uptake of genetic testing and the relatively high prevalence of *BRCA* mutations in advanced PCa, understanding their predictive utility is important to optimize treatment selection and sequencing. To date, androgen deprivation therapy (ADT) remains the backbone of treatment for mCRPC, although, several other agents and their combinations became available, including androgen receptor pathway inhibitors (ARPI) such as abiraterone and enzalutamide, taxane chemotherapy (docetaxel, cabazitaxel), prostate-specific membrane antigen (PSMA)-ligand treatment, and PARPi (23). However, data on the impact of *BRCA* mutation status on the efficacy of treatments beyond PARPi are scarce.

6. Objectives

6.1. Project I:

Considering the growing global utilization and uptake of MRI in the diagnostic pipeline of PCa, in our first project we aimed to comprehensively synthesize evidence to inform clinical practice and help devise a PCa screening strategy incorporating MRI information. Particularly, our goal was to summarize the currently available literature on the performance of PCa population-based screening strategies incorporating MRI, and to compare them to PSA-only-based screening.

6.2. Project II

In our second project, we aimed to assess the therapy predictive utility of *BRCA* mutations in patients with mCRPC. Specifically, we assessed the efficacy of various treatment modalities, including ARPI (abiraterone, enzalutamide), taxane-based chemotherapy (docetaxel, cabazitaxel), PSMA-ligand therapies, platinum-based chemotherapy, and PARPis in *BRCA*-positive mCRPC.

7. Methods

7.1. General considerations

To address our objectives, we performed systematic reviews and meta-analyses according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 guideline, and the *Cochrane Handbook* (32, 33).The study protocols were registered on PROSPERO (registration numbers: CRD42023423945; CRD42021285267; CRD42022287005).

7.2. Project I.

7.2.1. Eligibility criteria and outcome measures

To evaluate the performance of MRI-based screening strategies, we used the population, intervention, control, and outcomes framework (34). We included studies of men in the general population or those with elevated genetic risk for PCa, who were screened for PCa (population) who underwent MRI examination as part of the screening (intervention) and were compared with men screened for PCa using PSA alone (comparison). Studies were selected if they reported data in screening-like populations, while those addressing diagnostic test accuracy or those that enrolled preselected men to undergo biopsy were excluded. The primary endpoint was the cancer detection rate (CDR) of clinically significant PCa, defined as an International Society of Urological Pathology (ISUP) grade of 2 or higher (outcome). Secondary endpoints included the CDR of insignificant PCa (defined as ISUP grade 1), positive predictive values (PPVs) for detecting significant and insignificant PCa, MRI and biopsy indication, biopsy adherence, and complication rates. Moreover, we calculated CDRs using alternative definitions of significant (ISUP ≥3) and insignificant (ISUP 1-2) PCa. This meta-analysis was restricted to prospective observational or randomized studies.

7.2.2. Search strategy, study selection, and data collection

The MEDLINE (via PubMed), Embase, Cochrane/Central, Scopus, and Web of Science databases were queried through May 5, 2023. The search strategy included three key components: prostate cancer, MRI, and screening. After selection by two independent review authors, the following data were extracted from the eligible studies: general information; study population characteristics; details of the intervention and comparator,

including screening algorithm (MRI in first-line/sequential screening), sequence (biparametric/multiparametric), and type (1.5T/3T) of MRI; Prostate Imaging Reporting and Data System (PI-RADS) cut-off for the indication of biopsy (PI-RADS ≥3 or ≥4); type of biopsy approach (targeted + systematic/targeted only, cognitive/image-fusion); PSA cut-off; additional novel biomarkers in the screening pathway; and the outcomes of interest described previously (35). In cases where studies did not report the specified outcomes, two authors independently calculated them using the data provided within the studies. Any disagreements on study selection and data extraction were resolved through consensus with a third author. Sensitivity, specificity, and negative predictive value could not be evaluated because prostate biopsies were not performed in cases of negative screening test results. To address inconsistencies or overlapping data among studies, we adjusted the study samples.

7.2.3. Statistical analysis

Quantitative data synthesis was carried out with the packages `meta`, `metafor`, and `clubSandwich` of the R statistical software (R Core Team, 2019, Vienna, Austria, R version 4.1). For our calculations, we followed the methods recommended by the working group of the Cochrane Collaboration (33). For all statistical analyses, a p-value of less than, or equal to 0.05 was considered significant. Based on the likely heterogeneity of the studies included, we used random-effect models for our calculations (36, 37). To assess and compare CDR, PPV, MRI, biopsy indication rates, and adherence to biopsy of the different screening pathways, we calculated pooled event rates and odds ratios (OR) with 95% confidence intervals (CI) using the generalized mixed effect approach (38). Certain studies evaluated MRI and PSA rates in the same population, therefore, to gain pooled ORs, we performed a bivariate analysis of the logit transformed proportion pair using the `rma.mv()` function of the metafor package. In this calculation, the difference of the pooled logit proportions is equal to the logarithm of the OR. We exponentiated this difference and its confidence interval to get a pooled OR with 95% CI. We approximated the within-study correlations for studies using the same population via simulation. When the MRI and PSA-related rates were evaluated on different populations, we used 0 as the within-study correlation. After fitting the random effect bivariate model, we applied the robust correction implemented in the clubSandwich package. As a sensitivity analysis, we repeated the procedure with different imputed correlations. These analyses revealed

similar results. To assess the optimal timing of MRI in the screening pathway, we conducted separate analyses based on different PI-RADS cut-offs for indicating biopsy (≥3, ≥4) and MRI timing (primary/sequential tool). We utilized forest plots to visualize event rates and effect measures. To evaluate the moderator effect of different factors, type of MRI sequence, and biopsy technique we performed subgroup analyses. The minimum number of studies to perform a meta-analysis was three. Heterogeneity was assessed in the case of the pooled rates by calculating the I^2 measure and its CI. Publication bias could not be assessed due to the low number of articles (less than ten) for one outcome (39).

7.2.4. Risk of bias

For randomized and nonrandomized studies, the risk of bias (RoB) was evaluated according to the Cochrane Collaboration's RoB assessment (RoB2) and the Risk of Bias in Nonrandomized Studies of Interventions tools independently by two reviewers (40, 41). Disagreements were resolved via consensus with a third author.

7.3. Project II.

In our second project, we conducted separate systematic reviews and meta-analyses of standard therapies (abiraterone, enzalutamide, docetaxel) and later-line treatments (cabazitaxel, PSMA-targeted agents, PARPis, platinum) for PCa.

7.3.1. Eligibility criteria and outcome measures

Studies reporting PSA50, progression-free survival (PFS), or OS data from *BRCA* mutation-positive mCRPC patients who underwent standard first- (docetaxel, abiraterone, enzalutamide) or later-line (PARPi, platinum, cabazitaxel, PSMA-ligand alone or in combination) available treatment were considered eligible. Case reports, case series, cross-sectional studies, conference abstracts and reviews were excluded.

The primary endpoint of the studies was the PSA response rate, defined as at least a 50% decrease in serum PSA level during treatment (PSA50). Our secondary endpoints were PFS (composite of clinical, radiographic, biochemical progression or death), and OS.

First, to assess the proportion (PSA50) and median values (PFS, and OS), we used the CoCoPop framework, where the endpoints (Co-condition) were evaluated in the context

of administered treatments (Co-context) in the population with mCRPC (Pop-population) (34).

Then, to compare time-to-event data, we used the PICO framework, where the population (P) was mCRPC patients with *BRCA* mutations; the interventions and controls (I and C) were abiraterone/enzalutamide/docetaxel and PARPi/platinum/cabazitaxel/PSMA-ligand therapies; and the outcomes were PFS (O1) and OS (O2) (42).

7.3.2. Search strategy, study selection, and data collection

The Embase, MEDLINE (via PubMed) and CENTRAL (The Cochrane Central Register of Controlled Trials) databases were searched on the 17th of October 2021 for studies of abiraterone, enzalutamide and docetaxel, and on the 23rd of February 2022 for those assessing PARPi, platinum, cabazitaxel and PSMA-ligand therapies. After duplicates were removed, two independent review authors performed selection first by title and abstract, then by full text. All disagreements were resolved via a third reviewer. We calculated Cohen's kappa coefficient to evaluate inter-rater reliability during the selection process (43).

From the eligible articles, the following data were extracted by two authors independently: title, first author, the year of publication, study population, study period, countries, study design, main study findings, number of patients, patient demographics, data on mutations, interventions, outcomes. In addition, when available, we collected individual patient data. In addition, we collected individual patient data when available. If these were not reported, we contacted the corresponding authors for supporting information. In the case of inconsistent or overlapping data, we performed adjustments to the article samples. Disagreements were resolved via consensus with a third author.

7.3.3. Statistical analysis

Quantitative synthesis of data was carried out with the packages 'coxme', 'IPDfromKM', 'meta', 'survival' and 'survminer' of the R statistical software (v. 4.1.2.). For our calculations, we followed the recommendation of Harrer *et al.* (44). For all statistical analyses, a p value of ≤ 0.05 was considered significant. Different random-effect meta-analysis tools were applied depending on the type of outcomes. The minimum number of studies to perform a meta-analysis was three.

For our CoCoPop question, in the first study focusing on standard treatments, we applied the classical inverse variance method with logit transformation. We pooled the PSA50 response rates for each treatment line separately and compared the different treatments by applying subgroup analyses based on the type of intervention. For the second study, which examined later-line therapies, we used the generalized mixed-effect approach of Stijnen *et al.* to pool proportions (38). We pooled the PSA50 response rates for each treatment separately and compared the different treatments by applying subgroup analyses based on the type of intervention, type of study design, and PARPi agent. We calculated pooled event rates with 95% confidence and prediction intervals. To estimate τ^2, we used the Paule-Mandel method. Heterogeneity was assessed by calculating the I^2 measure, its confidence interval and the Cochrane Q test.

For our CoCoPop question, we performed a single-arm random-effect meta-analysis. Using the multivariate methodology of Combescure *et al.*, we created pooled survival curves with CI and assessed heterogeneity by calculating multivariable I^2 (45). Moreover, we also reported the random-effect median pool provided by the methodology applied. Creating pooled PFS and OS curves and calculating pooled medians with this methodology were feasible only for PARPis due to the low number of articles on other interventions. Articles reporting at least 20 patients were included in this analysis. Besides avoiding problems with small sample sizes, this limitation had the advantage that, in this way, calculations were performed exclusively on prospective trials.

For performing time-to-event analyses for our PICO question, we collected individual PFS and OS data from the studies according to the methodology described by Goodman-Meza *et al.* (46). When the individual patient data was not accessible, we used the WebPlotDigitizer tool (Version 4.5 Copyright 2010–2021) to read digitized Kaplan-Meier curves and then we applied the methodology of Guyot *et al.* to estimate individual patient time-to-event data (47). We performed a one-step random-effects meta-analysis on the data of the *BRCA*-positive patients. We estimated hazard ratios (HR) between the treatments by applying the mixed effects Cox Proportional Hazards model. Owing to the low number of articles reporting data on PSMA-ligand and cabazitaxel treatments, we were able to compare PARPi and platinum agents only. The Kaplan-Meier curves for each outcome are shown in a common figure. Publication bias could not be assessed due to the low number of articles (<10) for one outcome (39).

7.3.4. Risk of bias

The risk of bias was evaluated for each study according to the Joanna Briggs Critical Appraisal Checklist for Studies Reporting Prevalence Data, Cohort Studies, and Randomized Controlled Trials by two independent reviewers. Disagreements were resolved by a third author (48).

8. Results

8.1. Project I: MRI in prostate cancer screening.

8.1.1. Study selection and baseline characteristics

We identified 2037 studies, of which 1464 were screened after removing duplicates. Finally, from the 28 full-text selected studies, 12 and 8 comprising 80,114 individuals were eligible for qualitative and quantitative evidence synthesis, respectively (Figure 1). We identified four population-based randomized clinical trials, two prospective cohort studies, and three prospective pilot studies (Table 1) (49-58). Moreover, we included two studies that reported on the efficacy of MRI in a prescreened population (59, 60). We identified four studies that reported data on the use of novel molecular biomarkers and MRI in PCa screening (53, 56-58). Most publications included data on the use of MRI as a reflex test after PSA; however, three studies were identified reporting on up-front MRI (49, 54, 55). Five studies used biparametric MRI (bpMRI), and 8 included multiparametric MRI (mpMRI) (Table 2). As for the method of biopsy, seven studies used MRI targeted only, while six studies used additional systematic sampling (Table 2).

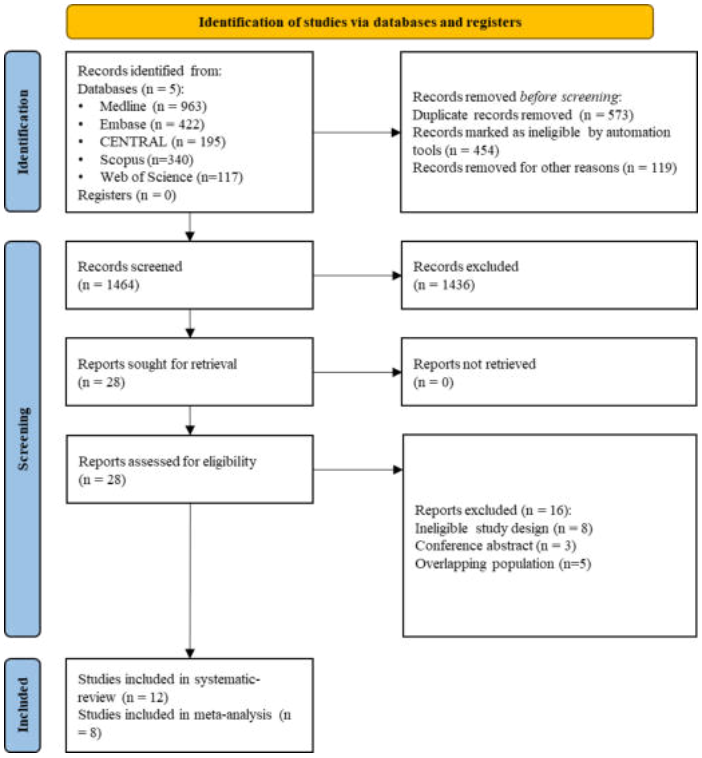


Figure 1 – PRISMA flowchart of study selection (MRI in PCa screening)

Table 1 – Characteristics of the included studies (MRI in PCa screening)

First Author (Study name)	Year	Country	Study design	Age of the screened men (median, IQR)	Number of screened
Eldred-Evans (49) (IP1-PROSTAGRAM)	2023	UK	Prospective cohort	57 (53-61)	All: 408 [a]
Hugosson (50) (Göteborg 2, 1st round)	2022	Sweden	RCT	56 (52-59)	Intervention: 11986 Comparator: 5994
Arsov (51) (PROBASE)	2022	Germany	RCT	45 (44-47) [d]	Intervention: 23341 Comparator: 23301
Eklund (52) (STHLM3-MRI)	2021	Sweden	RCT	66 (61-71)	Intervention: 929 [f] Comparator: 603 [f]
Nordström (53) (STHLM3-MRI)	2021	Sweden	RCT	66 (61-71)	Intervention: 1372 [h] Comparator: 921 [h]
Nam (55) (MVP – Pilot study)	2016	Canada	Prospective cohort	61 (55-68)	All: 47
Nam (54) (MVP)	2022	Canada	RCT	68 (±7.3) [i]	Intervention: 259 Comparator: 266
Grenabo Bergdahl (59) (Göteborg, 10th round – Pilot study)	2016	Sweden	Prospective cohort	69 (69-70)	All: 384
Alberts (60) (ERSPC, 5th round – Pilot study)	2018	Netherlands	Prospective cohort	73 (72-73)	All: 713 [j]
Rannikko (56) (ProScreen – Pilot study)	2022	Finland	Prospective cohort	64-65 [k]	All: 170
Benafif (57) (BARCODE1 – Pilot study)	2022	UK	Prospective cohort	61 (55-69) [l]	All: 307
Segal (58) (NCT02053805)	2020	Israel	Prospective cohort	54 (±9.8) [n]	BRCA1: 108 BRCA2: 80

Table 2 – Characteristics of screening strategies

First Author (Study name)	Details of MRI-based strategy (Intervention)			Details of PSA-based strategy (Comparator)	
	Indication of MRI	**MRI type**	**Method of biopsy**	**PSA cut-off**	**Type of biopsy**
Eldred-Evans (49) (IP1-PROSTAGRAM)	1st line screening and PSA ≥ 3ng/ml	bpMRI	Image fusion transperineal targeted	≥3ng/ml	Transperineal systematic
Hugosson (50) (Göteborg 2, 1st round)	PSA ≥ 3ng/ml	mpMRI	Cognitive transrectal targeted [b]	≥3ng/ml	Transrectal systematic [c]
Arsov (51) (PROBASE)	PSA ≥ 3ng/ml	mpMRI [e]	Image fusion transrectal targeted and systematic	NA	NA
Eklund (52) (STHLM3-MRI)	PSA ≥ 3ng/ml	bpMRI	Image fusion transrectal targeted and systematic [g]	≥3ng/ml	Transrectal systematic
Nordström (53) (STHLM3-MRI)	PSA ≥ 3ng/ml or Stockholm 3 score ≥ 0.11	bpMRI	Image fusion transrectal targeted and systematic	≥3ng/ml	Transrectal systematic
Nam (55) (MVP – Pilot study)	1st line screening	mpMRI	Cognitive transrectal targeted and systematic	NA	NA
Nam (54) (MVP)	1st line screening	bpMRI	Image fusion transrectal targeted and systematic	≥2.6ng/ml	Transrectal systematic
Grenabo Bergdahl (59) (Göteborg, 10th round – Pilot study)	PSA ≥ 3ng/ml	mpMRI	Cognitive transrectal targeted	≥3ng/ml	Transrectal systematic
Alberts (60) (ERSPC, 5th round – Pilot study)	PSA ≥ 3ng/ml	mpMRI	Image fusion transrectal targeted	≥3ng/ml	Transrectal systematic

Rannikko (56) (ProScreen – Pilot study)	PSA ≥ 3ng/ml and 4Kscore > 7.5%	mpMRI	Image fusion transrectal targeted	NA	NA
Benafif (57) (BARCODE1 – Pilot study)	Poligenic risk score ≥ 90th percentile	mpMRI	Image fusion transrectal targeted and systematic [m]	NA	NA
Segal (58) (NCT02053805)	Elevated age-stratified PSA [o]	mpMRI	Image fusion transrectal targeted	Elevated age-stratified PSA [o]	Transrectal systematic

Footnotes for Table 1 and 2

[a] All patients underwent screening with both PSA and MRI, therefore both MRI as 1st line and 2nd line (after PSA) screening tool was assessed.

[b] In case of negative MRI and a PSA level >10ng/ml systematic biopsy was performed. In order to assess the performance of targeted biopsy only we excluded cancers detected with systematic biopsy and negative MRI in the experimental arm of the study from our analyses.

[c] In case of positive MRI in the reference arm, targeted biopsy was performed in addition to systematic. To assess the performance of systematic biopsy only we excluded cancers detected with targeted biopsy in the reference arm of the study from our analyses.

[d] Reported as mean and range.

[e] MRI examination was not part of the PROBASE screening protocol since the trial was started before mpMRI was recommended for primary diagnosis of PCa in the EAU guidelines in 2019. However, data on MRI are available in 79.0% of participants and 114 out of 120 men (95%) underwent MRI/ultrasound fusion targeted and systematic biopsy. The Arm B of this study indicated prostate biopsy solely on the basis of rectal digital examination findings, therefore we did not include it in our analysis.

[f] The provided numbers represent patients with a PSA ≥ 3ng/ml, as randomization was performed after PSA pre-screening. Initially 12750 patients were screened with PSA.

[g] In case of negative MRI and a Stockholm 3 score ≥ 0.25 systematic biopsy was performed. To assess the performance of MRI-based biopsy only we excluded cancers detected with systematic biopsy on the basis of an elevated Stockholm 3 test.

[h] The provided numbers represent patients with a PSA ≥ 3ng/ml or a Stockholm 3 score ≥ 0.11, as randomization was performed after PSA and Stockholm 3 score-based pre-screening. Initially 12750 patients were screened.

[i] Reported as mean (±standard deviation). Number reported here represent the MRI arm of the study. The mean age of PSA arm was 68 (±7.8).

[j] Number of screened men was adjusted to “Arm 2” of the study.

[k] Only 64–65 year-old men were enrolled.

[l] Reported as mean and range.
[m] All patients with a polygenic risk score ≥ 90th percentile undergoes MRI and systematic biopsy. In case of positive MRI (PI-RADS score ≥ 3) targeted biopsy is added.
[n] Reported as mean (±standard deviation). This study enrolled germline breast cancer gene 1 or 2 positive patients.
[q] Elevated age-stratified PSA is defined as: ≥ 1 ng/ml for ages 40-50 years, ≥ 2 ng/ml for ages 50-60 years, ≥ 2.5 ng/ml for ages 60-70 years.

8.1.2. MRI as a sequential screening tool

We synthesized data from 57,081 men from six studies that utilized MRI as a reflex test after PSA measurement, with a PI-RADS score of 3 or higher as a cutoff as the biopsy indication (49-52, 59, 60).

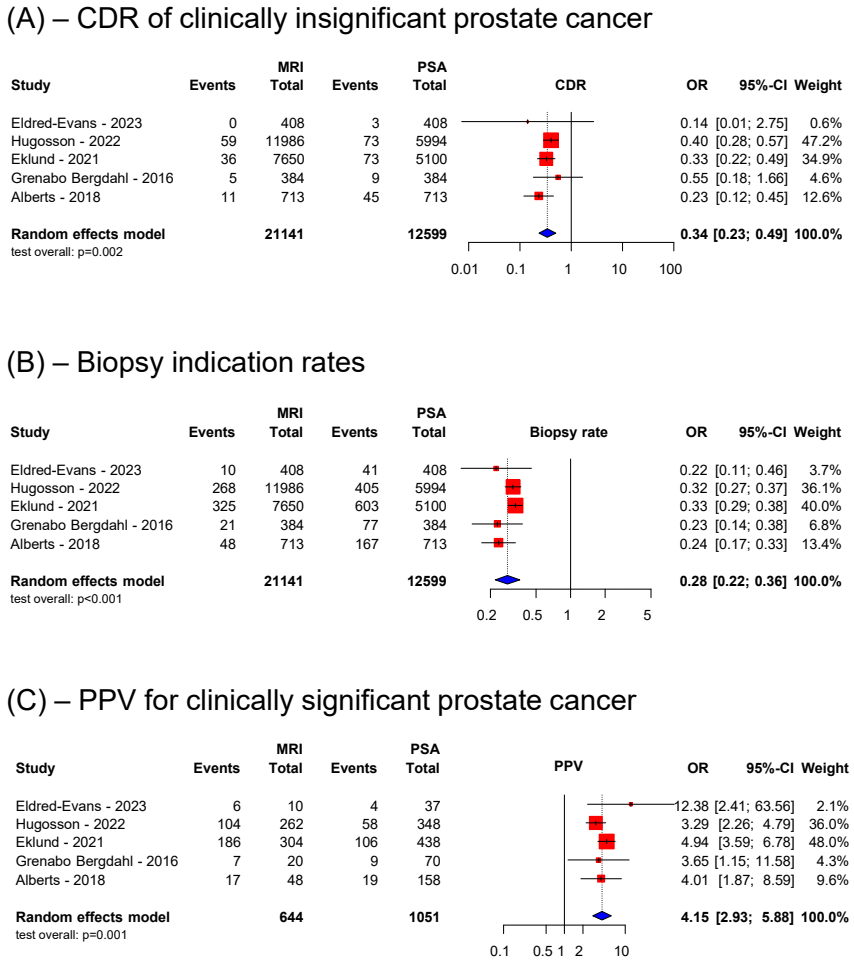


Figure 2 – Comparison of MRI-and standard PSA-based screening strategies in terms of prostate cancer detection (A), biopsy indication rate (B) and PPV (C). MRI is utilized as a reflex test after PSA measurement.

Table 3 and 4 summarizes pooled CDRs, PPVs, biopsy indication, and adherence rates. The number of men needed to screen to detect one significant PCa was 59 and 63 for PSA only and MRI-based strategies, respectively. Although we found no difference between the MRI-only and PSA-only screening methods in terms of clinically significant CDR (OR, 1.02; 95% CI, 0.75-1.37; $P = 0.9$), the MRI pathway was associated with lower odds of insignificant PCa detection (OR, 0.34; 95% CI, 0.23-0.49; $P = 0.002$) (Figure 2) (49, 50, 52, 59, 60). These trends in CDR remained similar when alternative definitions were applied for significant (ISUP ≥3: OR, 0.91; 95% CI, 0.54-1.52; $P = 0.4$) and insignificant PCa (ISUP 1-2: OR, 0.54; 95% CI, 0.23-1.29; $P = 0.09$). Furthermore, screening strategies that incorporated MRI had a higher PPV for detecting significant PCa (OR, 4.15; 95% CI, 2.93-5.88; $P = 0.001$) and a lower biopsy rate (OR, 0.28; 95% CI, 0.22-0.36; $P < 0.001$) than PSA-only-based ones (Figure 2) (49, 50, 52, 59, 60).

The pooled MRI rate was 8.5% (95% CI, 2.6%-24.8%; $I^2 = 100\%$) among the screened individuals, and adherence for biopsy indication was higher when MRI was utilized (OR, 4.61; 95% CI, 2.39-8.89; $P = 0.01$) (Figure 3) (49-52, 59, 60).

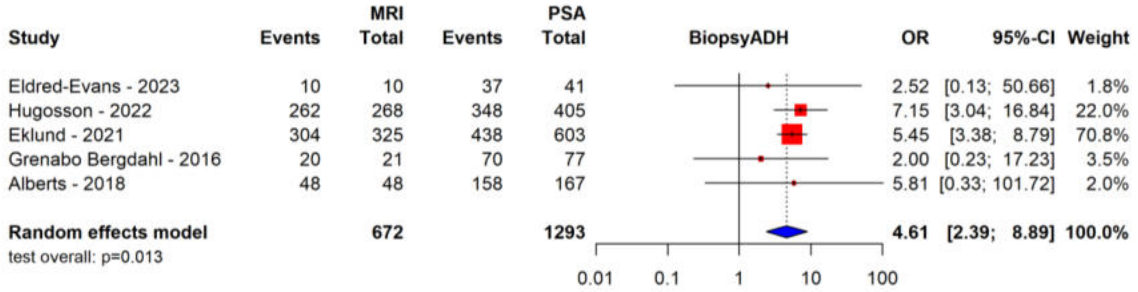


Figure 3 – Comparison of MRI-based and PSA-only screening pathways in terms of adherence rate to biopsy indication

To identify the high rate of heterogeneity among the studies and assess the moderator effect of different factors, we stratified studies based on the type of MRI sequence, biopsy method, and study design. Compared with mpMRI, the use of bpMRI was associated with a higher PPV for significant PCa (61.1% [95% CI, 26.5%-87.3%] *vs.* 34.8% [95% CI, 25.2%-45.7%]; $P < 0.001$) (Figure 4) and a lower PPV for insignificant PCa (11.5% [95% CI, 1.3%-55.1%] *vs.* 19.5% [95% CI, 12.3%-29.6%]; $P = 0.01$) (Figure 5), respectively, without heterogeneity across the subgroups. Moreover, we detected lower PPV for

insignificant PCa detection with targeted + systematic (*vs.* targeted) and image fusion (*vs.* cognitive) biopsies.

Table 3 – Diagnostic performance of screening strategies incorporating MRI

		Cancer detection rate (95% CI)		Positive predictive value (95% CI)	
		Significant PCa	**Insignificant PCa**	**Significant PCa**	**Insignificant PCa**
MRI sequential (PI-RADS 3-5)	**MRI**	1.1% (0.4-3.1%) I^2: 98%	0.4% (0.1-1.4%) I^2: 94%	41.9% (28.5-56.7%) I^2: 90%	16.3% (10.8-23.9%) I^2: 67%
	PSA	1.7% (1-2.8%) I^2: 86%	1.9% (0.7-4.6%) I^2: 96%	16.1% (10.4-24.2%) I^2: 76%	18.4% (11.9-27.3%) I^2: 74%
	MRI vs PSA (OR)	1.02 (0.75-1.37) p=0.86	0.34 (0.23-0.49) p=0.002	4.15 (2.93-5.88) p=0.001	1.0 (0.5-2.0) p=0.99
MRI sequential (PI-RADS 4-5)	**MRI**	1.2% (0.4-3.9%) I^2: 86%	0.4% (0.2-0.7%) I^2: 45%	48.9% (35.4-62.6%) I^2: 0%	21.1% (11.9-34.7%) I^2: 0%
	PSA	1.4% (0.4-4.7%) I^2: 87%	1.9% (0.2-17.5%) I^2: 98%	14.9% (9.5-22.7%) I^2: 15%	20.9% (7.7-45.5%) I^2: 74%
	MRI vs PSA (OR)	0.85 (0.49-1.45) p=0.23	0.23 (0.05-0.97) p=0.048	7.01 (1.76-27.98) p=0.03	0.99 (0.29-3.32) p=0.96
MRI primary (PI-RADS 4-5)	**MRI**	6.0% (0.6-39.4%) I^2: 92%	1.2% (0.2-7.3%) I^2: 55%	41.9% (16.1-73.0%) I^2: 57%	10.1% (2.2-35.9%) I^2: 0%
	PSA	NA	NA	NA	NA
	MRI vs PSA (OR)	NA	NA	NA	NA

Table 4 – Biopsy indication and adherence rate of screening strategies incorporating MRI

		Biopsy indication rate (95% CI)	Biopsy adherence rate (95% CI)
MRI sequential (PI-RADS 3-5)	**MRI**	2.9% (1.4-6.2%) I^2: 99%	95.9% (77.1-99.4%) I^2: 95%
	PSA	13.2% (7.3-22.8%) I^2: 98%	88% (75.1-94.6%) I^2: 93%
	MRI vs PSA (OR)	0.28 (0.22-0.36) p<0.001	4.61 (2.39-8.89) p=0.01
MRI sequential (PI-RADS 4-5)	**MRI**	2.4% (0.9-6.3%) I^2: 89%	98.7% (86.6-99.9%) I^2: 0%
	PSA	11.9% (2.9-38.2%) I^2: 99%	90.5% (72.2-97.2%) I^2: 76%
	MRI vs PSA (OR)	0.19 (0.09-0.38) p=0.01	4.68 (0.37-59.49) p=0.12
MRI primary (PI-RADS 4-5)	**MRI**	15.0% (3.1-49.7%) I^2: 91%	93.1% (48.1-99.5%) I^2: 0%
	PSA	18.1% (4.7-49.7%) I^2: 91%	NA
	MRI vs PSA (OR)	0.81 (0.23-2.87) p=0.53	NA

Footnotes for Table 3 and 4: We evaluated MRI as primary or sequential screening tool and PI-RADS cut-offs of 3 or 4 for the biopsy indication. Rates are represented in percentages, with 95% CI-s. Within-study heterogeneity is expressed by I^2 values. For the comparison of MRI- and PSA-based screening we calculated odds ratios (OR) with 95% CI-s.

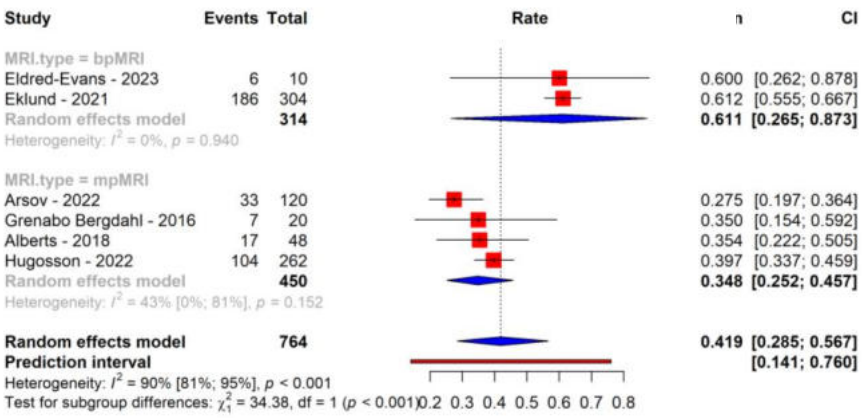


Figure 4 – Positive predictive values for the detection of clinically significant PCa of MRI-based screening – subgroups based on MRI sequence (biparametric *vs.* multiparametric)

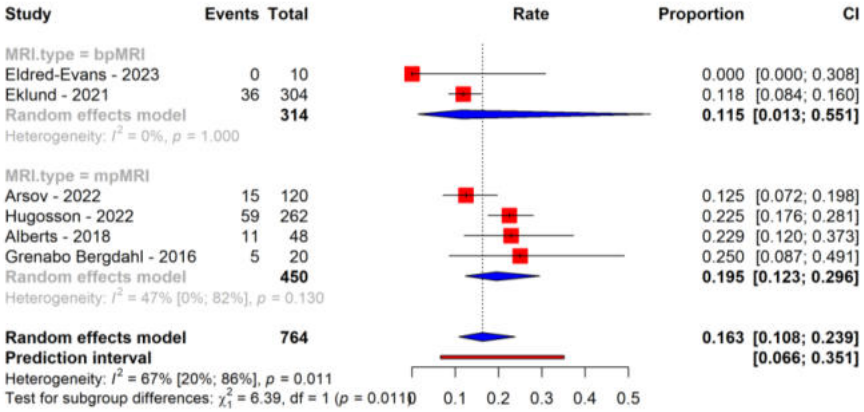


Figure 5 – Positive predictive values for the detection of clinically insignificant PCa of MRI-based screening – subgroups based on MRI sequence (biparametric *vs.* multiparametric)

Among the 19,501 patients who underwent a screening pathway using a PI-RADS cutoff of 4 or higher as a biopsy indication, we observed even lower odds of insignificant PCa detection (OR, 0.23; 95% CI, 0.05-0.97; $P = 0.048$) and biopsy (OR, 0.19; 95% CI, 0.09-0.38; $P = 0.01$) with a higher PPV (OR, 7.01; 95% CI, 1.76-27.98; $P = 0.03$) and similar CDR (OR, 0.85; 95% CI, 0.49-1.45; $P = 0.23$) for significant disease compared with standard PSA-only screening (Table 3 and 4, Figure 6) (49, 50, 60).

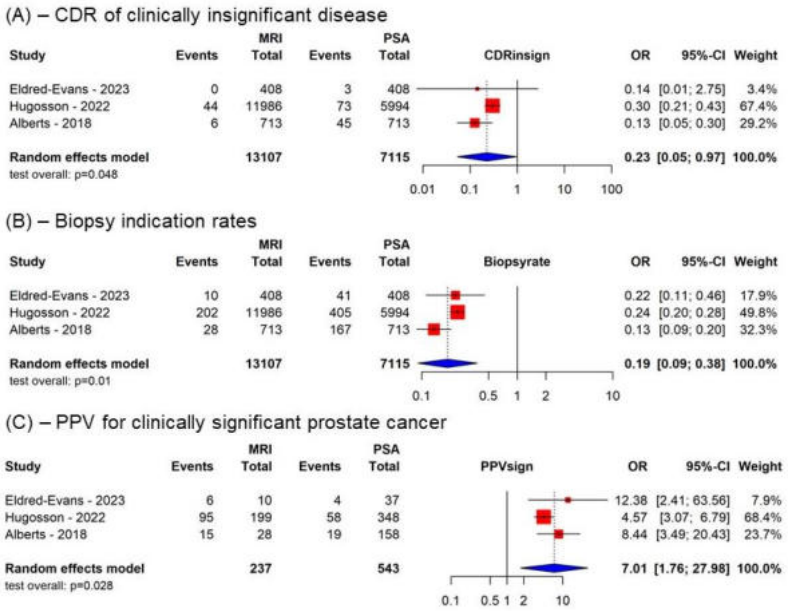


Figure 6 – Performance of magnetic resonance imaging (MRI) with a prostate imaging reporting and data system (PI-RADS) score of 4 or higher as a cut-off for biopsy indication

8.1.3. MRI as a first-line screening tool

We synthesized data from three articles involving 983 men evaluating the performance of MRI (PI-RADS ≥4) as a primary screening tool (49, 54, 55). Rates of clinically significant and insignificant disease were 6% (95% CI, 0.6%-39.4%; I^2: 92%) and 1.2% (95% CI, 0.2%-7.3%; I^2: 55%), respectively (Table 3 and 4). The PPV of upfront MRI to detect significant PCa was 41.9% (95% CI, 16.1%-73%; I^2: 57%) (Table 3 and 4). Due to limited data availability, comparison of MRI-based screening with PSA-based approaches was only feasible in terms of biopsy indication, which revealed no significant difference between the two pathways (OR, 0.81; 95% CI, 0.23-2.87; $P = 0.5$) (Table 3 and 4).

8.1.4. MRI-, and novel biomarker-based screening strategies

Four studies reported on the combination of MRI and novel biomarkers, however, given the heterogeneity between populations and interventions within studies, we did not perform a quantitative data synthesis (53, 56-58). In general, the use of novel biomarkers was associated with fewer insignificant PCa, while maintaining significant disease detection (53, 56). Moreover, MRI has been shown to be an effective screening tool in patients with a genetic predisposition – germline *BRCA* mutation carriers – for PCa (58).

8.1.5. Risk of bias

We identified a low overall RoB in most of the included studies for the CDR, PPV, MRI, and biopsy rates and biopsy adherence outcomes. Among randomized clinical trials, the intervention in the PROBASE trial was found to be biased, as MRI examination was not part of the screening protocol; however, MRI data were available in 79% of participants, and 114 of 120 men (95%) underwent MRI/ultrasonography fusion-targeted and systematic biopsy (51). Most observational studies displayed a low overall RoB, however some of them showed a moderate risk in categories related to study population.

8.2. Project II

8.2.1. Study selection and baseline characteristics

For our studies of standard and later-line treatments we screened 7979 and 6206 studies, respectively, yielding 16 and 23 publications comprising 348 and 901 *BRCA*-positive mCRPC patients eligible for qualitative and quantitative synthesis (Figure 7-8).

Table 5 to 8 includes the baseline characteristics of the included studies. We identified four randomized trials, seven prospective cohort studies, and five retrospective cohort studies evaluating abiraterone, enzalutamide, and docetaxel. For later-line treatments, we included four randomized trials, five phase 2 single-arm trials, three prospective and ten retrospective cohort studies, and one case series. We used individual patient data from 11 (61-71) and 17 studies (61, 66, 69, 72-85), in our analyses of standard and later-line treatments, respectively. Most publications included both germline and somatic mutations, and the test methods ranged from analysis of tumor tissue to various liquid biopsy techniques.

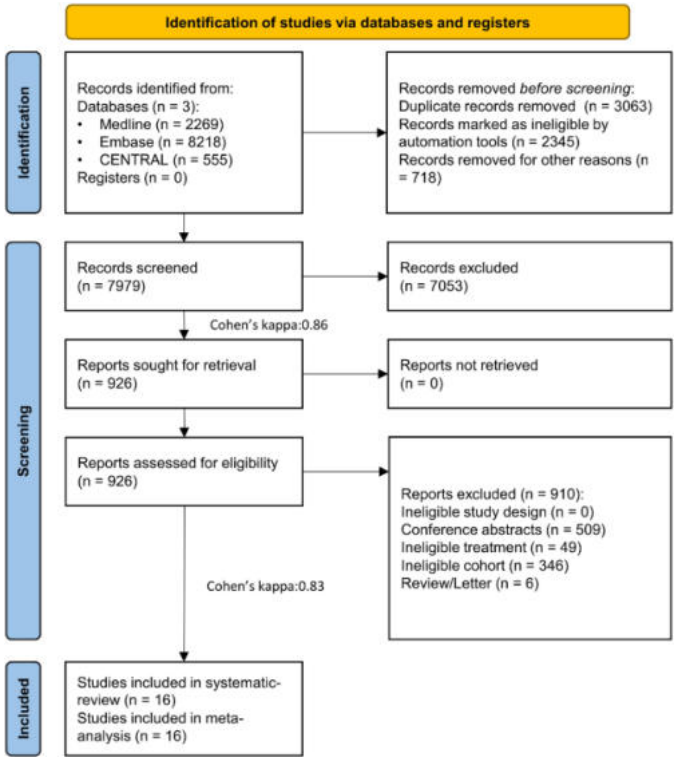


Figure 7 – PRISMA 2020 flowchart representing the study selection process (standard treatments – abiraterone, enzalutamide, docetaxel)

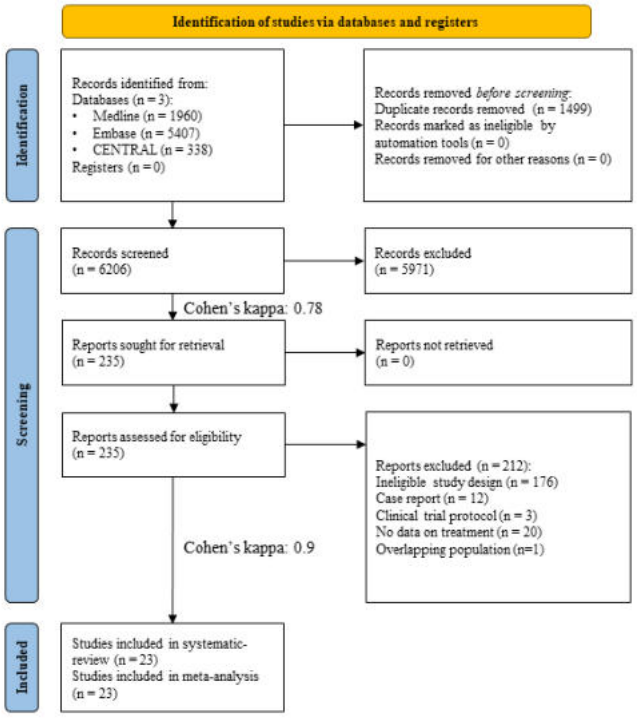


Figure 8 – PRISMA 2020 flowchart representing the study selection process (later-line treatments – platinum, PARPi, cabazitaxel, PSMA-ligand)

Table 5 – Baseline characteristics of the included studies (standard treatments – abiraterone, enzalutamide, docetaxel)

Author	Year	Country	Study type	No of patients	Age (median, range)	*BRCA* assessed	Mutation type
Annala (62)	2021	Canada	RCT	17	72 (57-85)	*BRCA1* *BRCA2*	germline somatic
Annala (63)	2018	Canada	RCT	27	72 (49-88)	*BRCA1* *BRCA2*	germline somatic
Annala (64)	2017	USA, Canada[a]	Observational cohort	13	63 (58–68) ǂ HRR cohort	*BRCA1* *BRCA2*	germline
Castro (86)	2019	Spain[a]	Observational cohort	18	64 (50-73)	*BRCA2*	germline
De Bono (61)	2020	UK[a]	RCT	58	67 (49–86) whole cohort	*BRCA1* *BRCA2*	germline somatic
Dong (66)	2021	China[a]	Observational cohort	15	69 (59-84)	*BRCA2*	germline somatic
Gallagher (68)	2012	USA	Retrospective	5	77 (59-88)	*BRCA1* *BRCA2*	germline
Hussain (69)	2018	USA[a]	RCT	5	N/A	*BRCA1* *BRCA2*	germline somatic
Kwon (73)	2021	USA, Canada[a]	Retrospective	65	61 (34-86)	*BRCA1* *BRCA2*	germline somatic
Mateo (70)	2018	USA, UK, Australia[a]	Retrospective	39	63 (55–66) ǂ	*BRCA1* *BRCA2*	germline
McKay (87)	2021	USA[a]	Observational cohort	10	N/A	*BRCA2*	somatic
Nientiedt (88)	2017	Germany	Retrospective	8	62 (8)‡	*BRCA2*	somatic
Sokolova (89)	2021	USA, Spain[a]	Retrospective	45	62 (55-67) ǂ	*BRCA2*	germline
Torquato (71)	2019	USA[a]	Observational cohort	12	65 (51-89)	*BRCA1* *BRCA2*	germline somatic
Wyatt (65)	2016	Canada	Observational cohort	3	57 (51-88)	BRCA2	germline
Zhao (67)	2022	China[a]	Observational cohort	8	N/A	BRCA1 BRCA2	germline somatic

Table 6 – Treatment characteristics in the included studies (standard treatments – abiraterone, enzalutamide, docetaxel)

Author	Assessed therapies	Available treatment line	Previous treatments allowed for mCRPC	IPD available
Annala (62)	Abiraterone Enzalutamide	1st 2nd	No	Yes
Annala (63)	Abiraterone Enzalutamide	1st	No	Yes
Annala (64)	Abiraterone Enzalutamide	N/A	N/A	Yes
Castro (86)	ARPI Docetaxel	1st	No	No
De Bono (61)	ARPI	2nd	Abiraterone Enzalutamide	Yes
Dong (66)	Abiraterone Docetaxel	1st 2nd	Abiraterone Enzalutamide Docetaxel	Yes
Gallagher (68)	Docetaxel	1st	No	Yes
Hussain (69)	Abiraterone	N/A	Patients with up to 2 prior chemotherapy regimens	Yes
Kwon (73)	Abiraterone Enzalutamide Docetaxel	1st 2nd	Abiraterone Enzalutamide Docetaxel	No
Mateo (70)	ARPI Docetaxel	1st 2nd	Abiraterone Enzalutamide Docetaxel	Yes
McKay (87)	Enzalutamide	1<	Abiraterone Docetaxel Sipuleucel T	No
Nientiedt (88)	Docetaxel	1st	No	No
Sokolova (89)	Abiraterone Enzalutamide Docetaxel	N/A	Abiraterone Enzalutamide Docetaxel	No
Torquato (71)	Abiraterone Enzalutamide	1st 2nd	Abiraterone Enzalutamide Docetaxel	Yes
Wyatt (65)	Enzalutamide	1st 2nd	Abiraterone Docetaxel	Yes
Zhao (67)	Abiraterone	1st	No	Yes

Footnotes for Table 5 and 6:

[a] Multicentric study

‡ Parameters represented as mean with standard deviation,

ǂ Parameters represented as median with interquartile range

† Study included only in systematic review

8.2.2. PSA50 response rates for abiraterone, enzalutamide and docetaxel

PSA50 response rates for the three treatments for the first and second-line settings were available for 211 patients from 13 articles (62, 63, 65-69, 71, 73, 86-89). Response rates regardless of treatment line for abiraterone, enzalutamide and docetaxel were 53% (CI: 35–71%; $I^2 = 36\%$), 56% (CI: 39–72%; $I^2 = 15\%$) and 47% (CI: 33–62%; $I^2 = 0\%$), respectively. When separating results according to treatment lines for mCRPC, we found greater differences in terms of PSA50 between the agents. Among the 97 patients treated in the first-line setting, PSA50 response rates were 52% (CI: 25–79%; $I^2 = 57\%$), 64% (CI: 43–80%; $I^2 = 0\%$), 55% (CI: 36–73%; $I^2 = 1\%$) for abiraterone, enzalutamide and docetaxel, respectively (Figure 9) (63, 66-68, 71, 73, 86, 89). Second-line data were available for 57 patients, PSA50 was generally lower compared to the first-line setting but showed similar distributions between abiraterone, enzalutamide and docetaxel therapies; 36% (CI: 17–61%; $I^2 = 3\%$), 46% (CI: 24–70%; $I^2 = 0\%$) and 42% (CI: 22–65%; $I^2 = 2\%$), respectively (62, 66, 71, 73, 89).

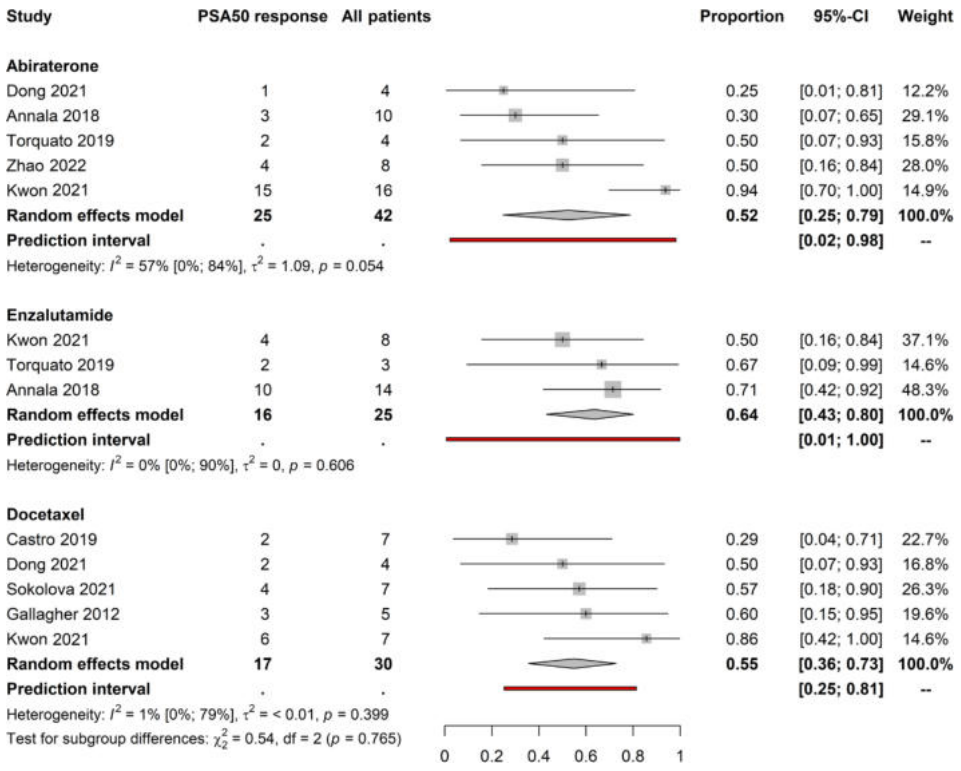


Figure 9 – PSA50 response rates of abiraterone, enzalutamide and docetaxel treated patients with mCRPC

8.2.3. PFS and OS analysis based on individual patient data for abiraterone, enzalutamide and docetaxel

By comparing the PFS rates of 78 *BRCA*-positive patients, we found a significantly lower hazard (HR: 0.47, CI: 0.27–0.83, $P = 0.01$) for progression in enzalutamide-treated compared to abiraterone-treated patients in the pooled first- and second-line setting (62, 63, 65-67, 69, 71). This tendency also appeared in the first-line setting; however, it did not reach statistical significance (HR: 0.56, CI: 0.27–1.17, $P = 0.1$, $n = 47$) (63, 65-67, 71). Comparisons of docetaxel with abiraterone (HR: 0.38, CI: 0.56–1.47, $P = 0.5$, $n = 86$) and enzalutamide with docetaxel (HR: 0.59, CI: 0.67–1.82, $P = 0.4$, $n = 68$) showed no significant differences in terms of PFS (regardless of treatment line) (62, 63, 65-67, 69-71). In the pooled analysis of first- and second-line treatments, the HR for OS was 1.41 (95% CI: 0.82–2.42; $P = 0.2$; n = 101) for enzalutamide vs. abiraterone, 1.65 (95% CI: 0.67–4.03; $P = 0.3$; n = 82) for docetaxel *vs.* abiraterone, and 1.69 (95% CI: 0.79–3.58; $P = 0.3$; n = 69) for enzalutamide *vs.* docetaxel (62, 63, 66, 68, 71, 73). In the first-line setting, we were able to compare enzalutamide *vs*. abiraterone, resulting in a HR of 1.91 (95% CI: 0.99–3.66; $P = 0.051$) in favor of abiraterone (63, 66, 71, 73).

Table 7 – Baseline characteristics of the included studies (later-line treatments – platinum, PARPi, cabazitaxel, PSMA-ligand)

First Author	Year	Study design	No of patients	Age (median, range)	BRCA test method
Kaufman (72)	2015	Phase II Single arm	8	71 (51-77)	N/A
Hussain (69) (NCI9012)	2018	Phase II RCT	14	68 (47-85) [a]	Tissue
Sokolova (89)	2021	Retrospective	14	62 (55-57) ǂ [a]	N/A
Kwon (73)	2021	Retrospective	65	61 (34-86) [a]	Germline and ctDNA or tissue
Dong (66)	2021	Prospective observational	7	67 (60-78)	ctDNA and tissue
De Bono (61) (PROfound)	2020	Phase III RCT	101	68 (47-86) [a]	ctDNA and tissue
Aldea (74)	2021	Retrospective	69	64 (45-75)	ctDNA or tissue or germline
Corn (90)	2019	Phase II RCT	36	68 (62–73) ǂ [a]	ctDNA
Cheng (91)	2015	Case series	3	66 (53-70)	Germline and ctDNA or tissue
Mateo (92) (TOPARP-A)	2015	Phase II Single arm	7	67 (41-79)	Germline and ctDNA or tissue
Pomerantz (75)	2017	Retrospective	8	53 (40-62)	Germline
Schmid (76)	2020	Retrospective	47	61 (37-78)	ctDNA; tissue
De Bono (77) (TALAPRO-1)	2021	Phase II Single arm	61	69 (63-72) ǂ	ctDNA, tissue; germline
Abida (78) (TRITON2)	2020	Phase II Single arm	115	72 (50-88)	Germline and ctDNA or tissue
van der Doelen (79)	2021	Prospective observational	2	71 (64-77) ǂ [a]	Tissue
Smith (80) (GALAHAD)	2022	Phase II Single arm	142	67 (63-73) ǂ	Germline and ctDNA or tissue
Mateo (81) (TOPARP-B)	2020	Phase II RCT	32	66 (7) ‡	Tissue
Privé (93)	2021	Prospective observational	8	64 (58-74) ǂ	Tissue and germline
Taza (82)	2021	Retrospective	123	67 (61-71) ǂ	N/A
Slootbeek (83)	2020	Retrospective	7	61 (51-69)	Tissue and germline
Mota (85)	2020	Retrospective	11	68 (63-73) ǂ [a]	Tissue and germline
Marshall (84)	2019	Retrospective	17	65 (61-70) ǂ	N/A
Lu (94)	2018	Retrospective	4	68 (52–73) [a]	Tissue and germline

Table 8 – Treatment characteristics in the included studies (later-line treatments – platinum, PARPi, cabazitaxel, PSMA-ligand)

First Author	Assessed therapies	mCRPC Treatment line	IPD available
Kaufman (72)	Olaparib	2≤	Yes
Hussain (69) (NCI9012)	Veliparib+abiraterone	2≤	Yes
Sokolova (89)	PARPi; platinum	N/A	No
Kwon (73)	Olaparib; carboplatin; cabazitaxel	1,2,3<	Yes
Dong (66)	Olaparib Platinum	N/A	Yes
De Bono (61) (PROfound)	Olaparib	2≤	Yes
Aldea (74)	Cabazitaxel	2≤	Yes
Corn (90)	Cabazitaxel Cabazitaxel+Carboplatin	2≤	No
Cheng (91)	Carboplatin	2≤	No
Mateo (92) (TOPARP-A)	Olaparib	3≤	No
Pomerantz (75)	Carboplatin	2≤	Yes
Schmid (76)	Cisplatin Carboplatin	1≤	Yes
De Bono (77) (TALAPRO-1)	Talazoparib	2≤	Yes
Abida (78) (TRITON2)	Rucaparib	3≤	Yes
van der Doelen (79)	Ac-PSMA	4≤	Yes
Smith (80) (GALAHAD)	Niraparib	3≤	Yes
Mateo (81) (TOPARP-B)	Olaparib	2≤	Yes
Privé (93)	Ac-PSMA Lu-PSMA	4≤	Yes
Taza (82)	PARPi	2≤	Yes
Slootbeek (83)	Carboplatin	N/A	Yes
Mota (85)	Cisplatin Carboplatin	2≤	Yes
Marshall (84)	Olaparib	N/A	Yes
Lu (94)	Olaparib Talazoparib	N/A	No

Footnotes for table 7 and 8:

[a] number representing broader study cohort than *BRCA*

‡ parameters represented as mean with standard deviation,

ǂ parameters represented as median with interquartile range

8.2.4. Oncologic efficacy of platinum vs. PARPi

We were able to synthesize PSA50 response rates for 545 PARPi- and 101 platinum-treated patients from 12 and eight studies, respectively (66, 73, 75-78, 80-85, 89, 91, 92, 94). Biochemical response rates for PARPis and platinum were 69% (CI: 53–82%; I^2: 62%, CI: 29–80%) and 74% (CI: 49–90%; I^2: 0%, CI: 0–68%), respectively (Figure 10), with no difference between the two agents ($P = 0.6$). Similarly, OS analysis of 550 *BRCA*-positive patients revealed no difference between platinum and PARPi treatments (HR: 0.86; CI: 0.49−1.52, $P = 0.6$) (61, 66, 72, 73, 75-77, 80-85).

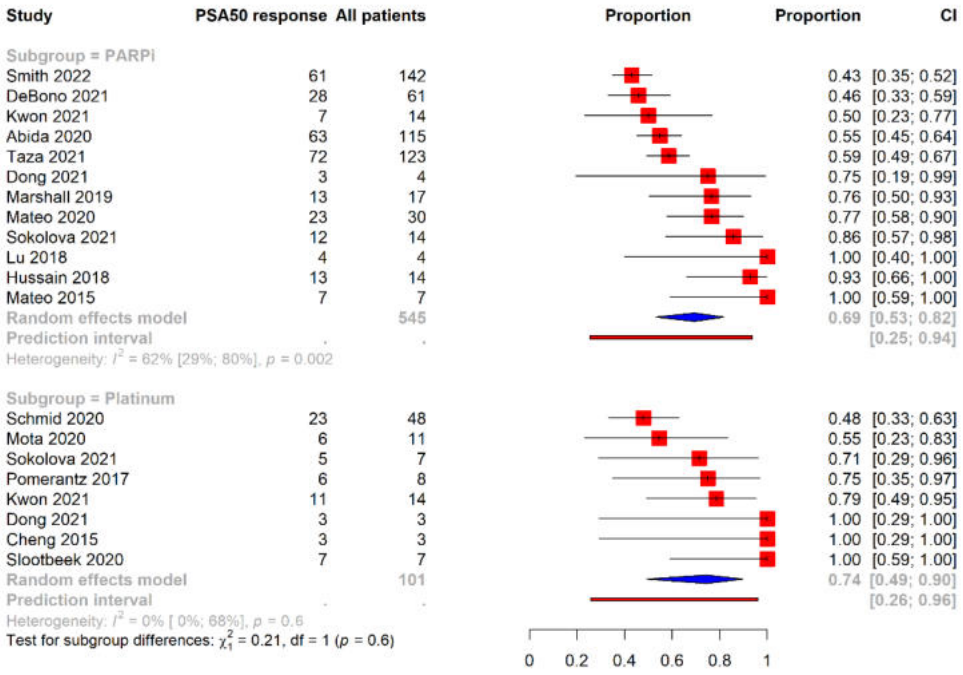


Figure 10 – PSA50 response rates of platinum and PARPi treated patients with mCRPC

8.2.5. Comparing the efficacy of different PARPis

To examine the different types of PARPi, we separated PSA50 results accordingly. We synthesized the data of 408 patients from ten studies and found that PSA50 response rates were 76% (CI: 54–90%; I2: 0%, CI: 0–75%), 46% (CI: 33–59%), 93% (CI: 66–100%),

55% (CI: 45–64%), and 43% (CI: 35–52%) for olaparib, talazoparib, veliparib (in combination with abiraterone acetate), rucaparib, and niraparib, respectively (Figure 11) (66, 69, 73, 77, 78, 80, 81, 84, 92, 94).

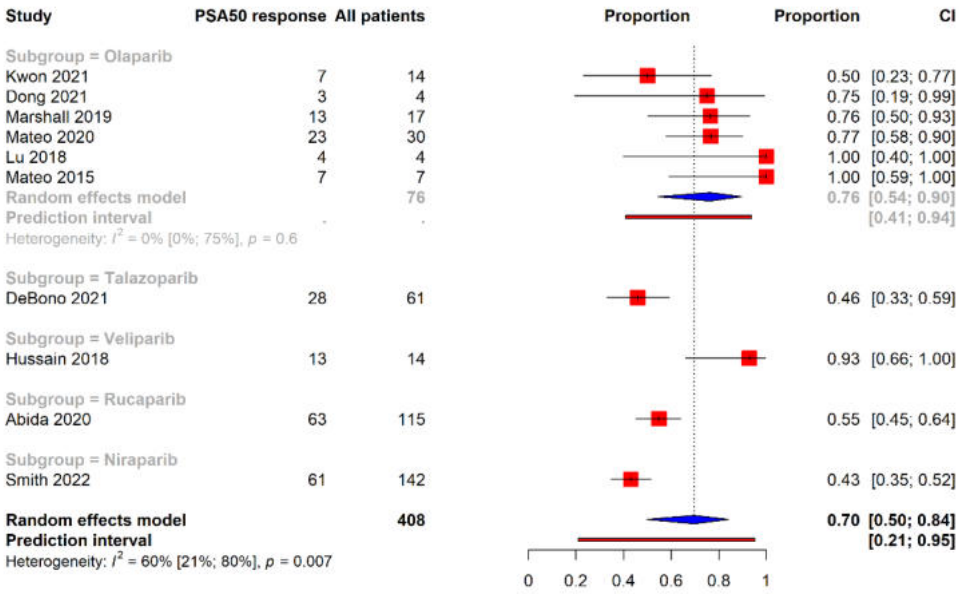


Figure 11 – PSA50 response rates of different PARPi compounds

The median pooled PFS and OS of PARPi was 9.9 months (CI: 8.5–12.2; I^2: 43%) and 18.3 months (CI: 14.3–24.6; I^2: 54%), respectively (61, 77, 78, 80-82). Pooling data exclusively from clinical trials showed median PFS and OS of 9.7 months (CI: 8.1–12.5; I^2: 38%) and 17.4 months (CI: 12.7–20.1; I^2: 36%), respectively, with low levels of heterogeneity (Figure 12) (61, 77, 78, 80, 81). To investigate the source of heterogeneity in terms of PSA50 of the PARPi cohort, we separated subgroups based on study type. We detected response rates of 82% (CI: 3–100%; I^2: 33%), 50% (CI: 37–63%; I^2: 18%, CI: 0–87%), 75% (19–99%), and 69% (CI: 43–86%; I^2: 30%, CI: 0–73%) in phase 2 randomized controlled trials, phase 2 single-arm trials, prospective cohorts, and retrospective studies, respectively, with a significant subgroup difference (P = 0.002).

8.2.6. PSA50 response to cabazitaxel- and PSMA-ligand therapy

For cabazitaxel and PSMA ligand treatments, we were able to analyze data only from four studies. Aldea *et al.* and Kwon *et al.* reported response rates of 27% and 33% with cabazitaxel, respectively (73, 74). For PSMA-ligand therapy, response rates were 38% and 100%, respectively (79, 93).

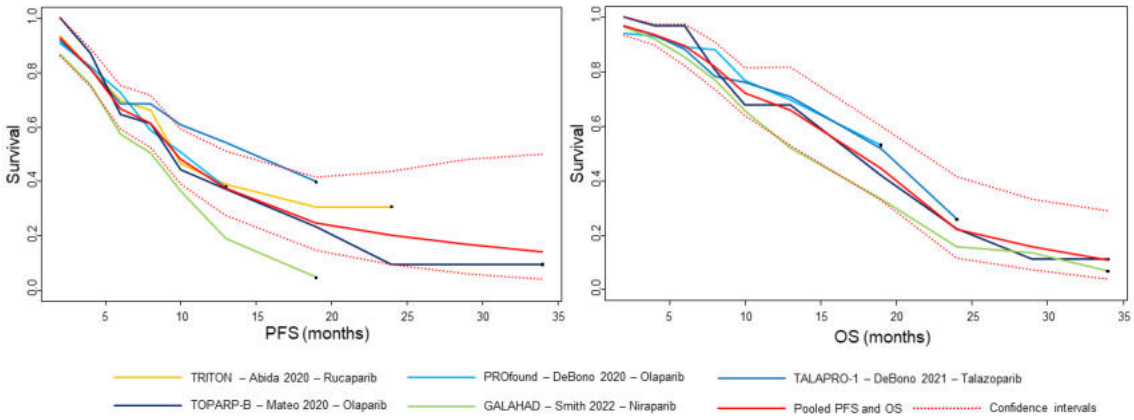


Figure 12 – PFS and OS of different PARPi compounds

8.2.7. Risk of bias

In the analysis of standard treatments, the Joanna Briggs Critical Appraisal Tools for Prevalence, Cohort, and Randomized Studies indicated a low overall RoB across studies reporting PSA50, PFS, and OS. Similarly, in the analysis of later-line treatments, a low RoB was identified in most included studies for PSA50, PFS, and OS outcomes. However, five studies showed a potentially elevated RoB, primarily due to their retrospective design (73, 75, 84, 91, 94). Overall, phase 2 and 3 randomized controlled trials, phase 2 single-arm trials, and prospective cohort studies demonstrated low RoB, whereas retrospective studies generally showed an intermediate RoB.

9. Discussion

9.1. Summary of findings, literature comparisons

9.1.1. Project I

Our systematic review and meta-analysis was the first to assess the performance of MRI in the setting of PCa screening, with several clinically relevant findings. First, these analyses suggested that MRI as part of sequential screening performs similarly to conventional PSA-based strategies in detecting clinically significant PCa, while reducing the number of detected insignificant cancers. Second, prebiopsy MRI was associated with a significantly reduced number of unnecessary prostate biopsies and enhanced the PPV for significant PCa detection compared with PSA-only screening with standard biopsies. Moreover, our data suggests modifying the threshold of offering prostate biopsy to a PI-RADS score of 4 or higher and the use of bpMRI-further reduce the rate of unnecessary biopsies, while not meaningfully compromising clinically significant PCa detection. Finally, the results of this study suggest that MRI as a first-line screening tool does not exhibit the benefits in reducing biopsy rates and the detection of insignificant PCa.

Our findings support the evidence that the use of MRI as a reflex test after PSA measurement is associated with decreased detection of insignificant PCa compared with PSA-only approaches. Thus, MRI is a useful tool to mitigate the limitations of PSA-based screening, including overdiagnosis of indolent PCa, which can be associated with overtreatment with avoidable complications associated with any therapy (95, 96). Meanwhile, the two screening strategies were similar in terms of CDR for clinically significant PCa.

Furthermore, use of MRI-based screening strategies was associated with higher PPV for detecting clinically significant PCa and a reduced number of biopsy indications. Based on our findings, the number of biopsies needed to detect 1 significant PCa was 2 and 6 with MRI-based and PSA-only screening strategies, respectively. These findings are particularly notable, given the risks of bleeding, infection, discomfort, and costs associated with prostate biopsy, as well as the psychological burden of screening-triggered workup (97, 98). Moreover, avoiding biopsy and following up patients with negative MRI results were shown to be a safe approach in screening (99, 100). According to the data presented, patients are more willing to undergo biopsy when the indication is

supported by MRI results, which is an important factor in achieving better outcomes and a more equal distribution of health care resources (9, 101, 102). In modeling studies, compared with standard PSA-based screening, integrating MRI in the PCa screening pipeline is associated with an improved benefit-harm ratio, quality of life, cost-effectiveness, and environmental effect (103, 104). Accordingly, our results endorse these findings, suggesting that MRI is effective at identifying individuals who are most likely to require further evaluation and biopsy, potentially reducing the burden on health care resources and sparing patients from having to undergo unnecessary invasive procedures.

This study summarizes performance characteristics of MRI-based screening across PI-RADS cut-offs for biopsy selection, different sequences (multiparametric or biparametric), biopsy methods (targeted only or targeted + systematic), and fusion types (cognitive or image fusion). According to our results, implementing a PI-RADS score of 4 or higher as a cut-off for biopsy selection is further associated with a reduced number of insignificant cancers detected and biopsies performed. Additionally, the choice of MRI sequence, whether biparametric or multiparametric, is an important aspect of screening. Shorter bpMRI protocols are faster, more cost-effective, and are associated with reduced exposure to contrast material, making them valuable in the screening process (105, 106). However, at the same time, interpretation of bpMRI can be more challenging, requiring a higher level of radiologist expertise (107). We found that bpMRI as compared to mpMRI is associated with a higher PPV for detecting significant PCa, which may be attributable to identifying larger, more conspicuous lesions in the absence of contrast (105, 108). Lastly, we examined the role of biopsy approach on MRI-based screening outcomes. These results revealed no significant differences in terms of CDR and PPV for significant disease between the targeted-only and targeted + systematic biopsy techniques, as well as between image fusion and cognitive biopsy methods. However, the targeted + systematic and image-fusion biopsies demonstrated a lower PPV for detecting clinically insignificant PCa. Our findings suggest that a screening pathway incorporating bpMRI following PSA measurement coupled with a PI-RADS score of 4 or higher cut-off for biopsy selection may be a promising strategy for increasingly accessible and cost-effective screening.

Our study also highlights the importance of considering the timing and type of MRI and biopsy in the screening process. While MRI following PSA prescreening (sequential pathway) demonstrated numerous advantages compared with PSA-only

strategies, up-front MRI as a primary tool did not appear to exhibit the aforementioned benefits in terms of biopsy rates and insignificant PCa detection; however, it was associated with high CDR for significant PCa. Although these results are limited by the lack of data for formal statistical comparison, this suggests that while MRI is valuable for refining the selection of patients for biopsy, its use as a primary screening tool needs to be further assessed in the future. Interestingly, among men younger than 55 who harbor *BRCA* germline alterations, upfront MRI has been demonstrated to have the highest clinical benefit, highlighting its diagnostic value for patients with a genetic predisposition for PCa (58).

9.1.2. Project II

Our two systematic reviews and meta-analyses are the first to comprehensively assess the oncologic efficacy of both standard (abiraterone, enzalutamide, docetaxel) and later-line treatments (PARPi, platinum chemotherapy, PSMA-ligand) in *BRCA* mutation-positive mCRPC patients, yielding several important findings. First, we confirmed that standard treatments, such as abiraterone, enzalutamide, and docetaxel are effective in this molecularly defined subgroup, although with some notable differences. Second, our results demonstrate that different PARPis have comparable oncologic efficacy. Finally, we found that platinum-based chemotherapy offers oncologic outcomes similar to PARPi.

BRCA-positive PCa represents a distinct molecular subtype, typically with earlier onset and more aggressive behavior (18-20). With higher sensitivity to PARPi treatments, these cases have different therapeutic sensitivity, suggesting that they may benefit from different treatment strategies. Therapeutic response to standard treatments in *BRCA*-positive patients has been previously reported, but only two studies directly compared abiraterone, enzalutamide, and docetaxel in this population, with conflicting results. While Sokolova *et al.* reported similar PSA50 responses across the three agents, Kwon *et al.* observed higher PSA50 rates and longer OS with abiraterone (73, 89). However, most studies compare outcomes of *BRCA*-positive *vs.* -negative PCa patients, therefore provide only prognostic information, rather than predictive data on treatment response. Such comparisons do not inform which therapies are most effective specifically for *BRCA*-positive patients and therefore are not capable of guiding individualized treatment decisions (109). To determine the optimal therapy for these patients, direct, head-to-head

comparisons of treatment options within this molecularly defined subgroup are needed. Our analysis, based on 348 *BRCA*-positive mCRPC patients, found the highest PSA50 response rate (64%) and longest PFS with enzalutamide, suggesting a potentially greater therapeutic effect of this androgen receptor targeted agent. Interestingly, seemingly in contrast, enzalutamide-treated patients tended to have shorter OS than those receiving abiraterone, a finding likely influenced by treatment sequencing and crossover. In particular, prior data suggests reduced efficacy of abiraterone when administered after enzalutamide, while the reverse sequence (abiraterone followed by enzalutamide) appears more favorable (62, 63). Our meta-analysis included patients from the above-mentioned trial, a significant number of patients received crossover between abiraterone and enzalutamide, which may explain the OS benefit in the first-line abiraterone-treated patients. A similar evaluation for docetaxel was not possible, because of the low numbers of patients with first-line docetaxel treatment. Nevertheless, considering the limitations of the available studies, our results should be considered hypothesis-generating, providing a basis for further prospective data collection.

Regarding PARPi, our findings demonstrate consistent oncologic efficacy across different compounds, including olaparib, niraparib, rucaparib, and talazoparib. While olaparib and veliparib showed the highest PSA50 rates, this may reflect higher dosing in earlier-phase trials (TOPARP-B), retrospective study design, and combination strategies (NCI9012) rather than intrinsic superiority (69, 92). Pooled median PFS and OS across agents were 9.7 and 17.4 months, respectively, with low heterogeneity, suggesting a class effect, highlighting that different PARPi agents have similar efficacy despite their distinct pharmacodynamic and pharmacokinetic properties (110). Importantly, PSA50 responses in real-world retrospective cohorts were comparable to those observed in prospective trials, suggesting that PARPis are effective in real-world clinical settings as well; however, a potential bias arising from retrospective studies should be taken into account.

Notably, our results can provide valuable information to contemporary trials combining PARPi with ARPI. The rationale of combining the two agents originates from the identification of the crosstalk between the AR and DNA repair pathways, which led to the hypothesis that ARPI may induce “synthetic lethality” in HRR deficient PCa-s. In other words, ARPI may augment the effect of HRR deficiency, resulting in synergistic effects in combination with PARPi (25-27). However, despite our results demonstrating

consistent PARPi efficacy, the outcome of phase III clinical trials assessing the combination of PARPi with ARPI were conflicting. For example, the combination of niraparib and abiraterone failed to show an OS benefit even in *BRCA*-positive patients, suggesting that (beside other potential confounders) while PARPis may have class-level efficacy, the choice of ARPI partner could significantly influence outcomes (111, 112) . Further indirect comparisons suggest a potential superiority of the talazoparib–enzalutamide combination, though these findings are limited by differences in trial design, methodological issues, patient selection, and molecular stratification (111). Nevertheless, our results demonstrating consistent PARPi efficacy and a possible advantage of enzalutamide over abiraterone in first-line treatment of *BRCA*-positive mCRPC patients, support further investigation of enzalutamide–PARPi combinations in this molecularly defined population.

A novel and clinically relevant result of our analysis is the comparable efficacy of platinum-based chemotherapy and PARPi in *BRCA*-positive mCRPC. Both agents produced high PSA50 response rates and similar OS outcomes, suggesting platinum is a valid treatment option for this molecular subgroup. This aligns with preclinical data indicating that *BRCA*-deficient tumors are sensitive to DNA crosslinking agents such as platinum (22). Moreover, considering the growing utilization of genetic testing and PARPis, treatment selection for patients with *BRCA*-positive mCRPC after progression on PARPi is of increasing clinical importance, as data supporting potential cross-resistance between the two compounds are available (83, 85). We identified two small retrospective studies assessing the sequencing of these agents, suggesting platinum remains active even after PARPi progression, however, it is more effective before PARPi therapy. To date, two small pilot trials (NCT02311764 and NCT02598895) are ongoing to evaluate platinum efficacy in this setting and will help establish its place in the treatment algorithm.

Later-line treatments such as cabazitaxel and PSMA-ligand therapy also warrant attention. Our findings support the favorable efficacy of cabazitaxel in *BRCA*-positive patients, although retrospective data suggest that prior PARPi exposure may reduce its efficacy (74, 90). Aldea *et al.* reported no responses to cabazitaxel in *BRCA*-mutated patients previously treated with PARPis, suggesting potential cross-resistance that should be investigated prospectively (74). As for PSMA-radioligand therapy, emerging evidence

indicates that HRR-deficient tumors may be more sensitive to radiation, possibly due to impaired DNA repair. Preclinical models and early clinical data have shown promising responses in *BRCA*-positive patients, though findings are inconsistent and based on small cohorts (17, 22, 113). The limited available literature data does not allow drawing a clear conclusion on the potential beneficial effects of PSMA-ligand treatment in *BRCA*-positive mCRPC patients, and further prospective studies are needed. The phase 1 LuPARP study, which evaluates the safety of olaparib in combination with 177Lu-PSMA in patients with mCRPC, may provide valuable in this field.

9.2. Strengths

9.2.1. Project I

This study is the first of its kind, to comprehensively evaluate MRI performance in the context of PCa screening, synthesizing data across different MRI sequences, PI-RADS thresholds, and biopsy methods. The inclusion of high-quality prospective studies and the focus on clinically meaningful outcomes, such as detection rates, biopsy avoidance, and adherence enhance the robustness and relevance of the findings.

9.2.2. Project II

This project was the first to comprehensively compare the efficacy of abiraterone, enzalutamide, docetaxel, cabazitaxel, PARPi, platinum, and PSMA-radioligand therapies in *BRCA* mutation-positive mCRPC patients. The inclusion of well-designed prospective trials with comparable patient selection criteria, alongside the application of robust statistical methods, enhances the reliability of our findings. Furthermore, this is the first analysis to demonstrate similar survival outcomes across different PARPis, adding important insights to treatment selection in this molecular subgroup. Finally, a novel and sound statistical methodology based on individual or estimated individual patient data was used to synthesize data.

9.3. Limitations

9.3.1. Project I

The primary limitation of our study is the relatively low number of articles that could be included; therefore, subgroup evaluation, heterogeneity, and publication bias assessment were limited. As no biopsy was performed in case of a negative MRI result, sensitivity,

specificity, and negative predictive values could not be assessed. Most of the studies assessed a Scandinavian population, limiting the generalizability of our findings. Safety and long-term survival data could not be synthesized, limiting the full-scale interpretation of our results. Finally, the optimal intensity and interval of MRI-based screening rounds have yet to be established, which require consideration of trade-offs regarding frequency of procedures, cancer detection, and associated costs.

9.3.2. Project II

This study has several limitations. First, the relatively low number of *BRCA*-positive patients, particularly for cabazitaxel and PSMA-ligand treatments limits the statistical power and generalizability of some findings. Second, the lack of prospective, interventional studies, especially for abiraterone, enzalutamide, docetaxel and platinum-based therapies, represents a major constraint. Third, PFS was not uniformly defined across the included studies, introducing potential measurement bias. Fourth, evolving recommendations for *BRCA* testing over the past decade may contribute to bias in retrospective studies. Additionally, due to small sample sizes, we were unable to stratify results by sequencing method (*e.g.*, primary tissue *vs.* liquid biopsy) or mutation type (germline *vs.* somatic). Notably, liquid biopsy–based detection using cell-free DNA can yield false-positive or false-negative *BRCA* findings, particularly in the context of low tumor burden or interference from clonal hematopoiesis of indeterminate potential (114, 115). Finally, heterogeneity in study design, patient selection, baseline characteristics, endpoint definitions, and genetic testing methods (*e.g.*, genes tested, mutation origin, sequencing platforms) may also impact the reliability and comparability of our results, especially in retrospective datasets.

10. Conclusions

10.1. Project I – Integration of MRI in prostate cancer screening

Our results suggest that prostate MRI with targeted biopsies is an effective strategy for the early detection of PCa. We found that MRI mitigates pitfalls of standard PSA-based strategies, as it is associated with fewer unnecessary biopsies and helps to avoid the detection of insignificant cancers while not compromising clinically significant disease detection. Considering these results, we need to reassess our approach to population-based PCa screening. However, the optimal setup of MRI and biopsy scheme in the screening process requires further evaluation.

10.2. Project II – *BRCA* as a predictive biomarker

Our findings confirm that *BRCA*-positive mCRPC patients respond to standard first-line treatments, including abiraterone, enzalutamide, and docetaxel, with enzalutamide showing the most favorable outcomes in terms of PSA response and PFS. However, this observation requires validation in prospective, molecularly selected interventional trials. We also demonstrated that different PARPis yield comparable PFS and OS, and that their efficacy appears similar to that of platinum-based chemotherapy in this patient population. These results support platinum as a valid treatment option for *BRCA*-mutated mCRPC. Nevertheless, head-to-head comparisons in biomarker-driven prospective trials are essential to establish the optimal therapeutic strategy.

11. Implementation for practice

11.1. Project I

The findings support integrating MRI following PSA prescreening into PCa screening pathways to reduce unnecessary biopsies and the detection of insignificant cancers without compromising the detection of clinically significant disease. Adopting bpMRI protocols and using a PI-RADS score ≥4 as a threshold for biopsy could enhance efficiency, reduce harm, and improve patient acceptance of screening interventions.

11.2. Project II

These findings support the integration of platinum-based chemotherapy as a viable treatment option for *BRCA*-positive mCRPC patients, particularly after progression on PARPis. Given its comparable efficacy, platinum may serve as a valuable component in the treatment sequence for this molecularly defined subgroup.

12. Implementation for research

12.1. Project I

Our study highlights key areas for future research, including the optimal biopsy technique (targeted-only *vs.* targeted + systematic), the most effective fusion method, and a more detailed cost-effectiveness analysis of MRI-based screening. Additionally, investigations into the long-term survival outcomes and biological behavior of PCas detected through MRI-targeted strategies are crucial to guide treatment decisions. Furthermore, differences in oncologic risk profiles have been observed between PCa cases diagnosed via MRI-based targeted biopsy and those identified through standard biopsy methods (116, 117). These findings underscore the need for further research to elucidate the behavior of PCa identified with MRI and targeted biopsy and their implications for treatment strategies.

12.2. Project II

Our results highlight the need for prospective, biomarker-driven clinical trials directly comparing platinum-based chemotherapy with PARPis, as well as head-to-head comparisons of standard treatments: abiraterone, enzalutamide, and docetaxel in *BRCA*-positive mCRPC patients. Future studies should also focus on optimizing the sequencing of these agents and identifying predictive markers of platinum sensitivity to guide individualized treatment strategies. Furthermore, additional data on cabazitaxel and PSMA-radioligand therapies are needed, considering the increasing clinical utilization of PSMA-targeted treatments.

13. Implementation for policy makers

13.1. Project I

For stakeholders our data suggests that MRI-based screening may improve the benefit-harm balance, cost-effectiveness, and resource allocation in PCa screening programs and further endorses the new screening initiatives of the European Union (118). These insights can inform guidelines, reimbursement decisions, and investments in radiological infrastructure and training to ensure equitable and effective screening.

13.2. Project II

These findings underscore the importance of incorporating *BRCA* genetic testing into routine clinical pathways for advanced PCa to enable molecularly guided treatment decisions. Reimbursement and access policies should support the use of platinum-based chemotherapy and PARPis in *BRCA*-positive mCRPC, alongside efforts to fund prospective, biomarker-driven trials. Additionally, investment in infrastructure for genomic testing and data integration will be essential to support personalized oncology care and improve outcomes in this high-risk patient population.

Moreover, two of our three publications have been incorporated into the 2025 edition of the EAU Prostate Cancer Guidelines, already shaping urological practice and policy (119, 120).

14. Future perspectives

14.1. Project I

Future studies should focus on defining the most effective and cost-efficient MRI-based screening pathways, including clarifying the role of bpMRI versus mpMRI and the ideal biopsy strategy following MRI. There is also a need to evaluate MRI-based screening in diverse populations, assess long-term oncologic outcomes, and explore its potential in personalized screening, particularly in genetically high-risk groups, such as *BRCA* mutation carriers. Additionally, the integration of novel biomarkers in the screening pathway is increasingly studied to further improve the harm-benefit ratio of screening (121). Since the publication of our study, detailed results from the BARCODE-1 and ProScreen trials have been reported, and we now plan to further evaluate the efficacy, cost-effectiveness, and economic impact of the combined PSA–biomarker–MRI screening approach (121-123). Finally, the integration of artificial intelligence into MRI interpretation may further enhance accuracy and accessibility (124, 125).

14.2. Project II

Ongoing trials are evaluating the efficacy of platinum-based chemotherapy in *BRCA*-positive mCRPC, aiming to clarify its role and optimal sequencing especially in the context of PARPi. In parallel, several studies are investigating PARPis and their combination with ARPI in earlier disease settings, which can potentially reshape treatment algorithms (126, 127). Future research should focus on integrating genomic profiling, identifying predictive markers for platinum response, and refining combination strategies to improve outcomes in this molecularly defined subgroup, even at earlier stages.

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castration-sensitive prostate cancer. Future oncology (London, England). 2024;20(9):493-505.

16. Bibliography of the candidate's publications

16.1. Publications related to the thesis

1. **Fazekas Tamas,** Shim Sung Ryul, Basile Giuseppe, Baboudjian Michael, Koi Tamas, Przydacz Mikolaj, Abufaraj Mohammad, Ploussard Guillaume, Kasivisvanathan Veeru, Rivas Juan Gomez, Gandaglia Giorgio, Szarvas Tibor, Schoots Ivo, van den Bergh Roderick, Leapman Michael, Nyirady Peter, Shariat Shahrokh, Rajwa Pawel *Magnetic Resonance Imaging in Prostate Cancer Screening: A Systematic Review and Meta-Analysis*
JAMA ONCOLOGY 10: 6 pp. 745-754., 10 p. (2024)
Publication: 34788748 | Journal Article (Survey paper) | Scientific
Scopus - Cancer Research SJR indicator: **D1**
Scopus - Oncology SJR indicator: D1
IF: 20,1

2. **Fazekas, Tamás**, Széles Ádám D, Teutsch Brigitta, Csizmarik Anita, Vékony Bálint, Kói Tamás, Ács Nándor, Hegyi Péter, Hadaschik Boris, Nyirády Péter, Szarvas Tibor *Poly (ADP-ribose) Polymerase Inhibitors Have Comparable Efficacy with Platinum Chemotherapy in Patients with BRCA-positive Metastatic Castration-resistant Prostate Cancer. A Systematic Review and Meta-analysis*
European Urology Oncology 7: 3 pp. 365-375., 11 p. (2024)
Publication: 34153931 | Journal Article (Survey paper) | Scientific
Scopus - Medicine (miscellaneous) SJR indicator: **D1**
Scopus - Oncology SJR indicator: D1
Scopus - Radiology, Nuclear Medicine and Imaging SJR indicator: D1
Scopus – Surgery / Urology SJR indicator: D1
IF: 9,3

3. **Fazekas T.,** Széles Á.D., Teutsch B., Csizmarik A., Vékony B., Váradi A., Kói T., Lang Z., Ács N., Kopa Z., Hegyi P., Hadaschik B., Grünwald V., Nyirády P., Szarvas T. *Therapeutic sensitivity to standard treatments in BRCA positive metastatic castration-resistant prostate cancer patients — a systematic review and meta-analysis*
PROSTATE CANCER AND PROSTATIC DISEASES 26: 4 pp. 665-672., 8 p. (2023)

Publication: 33421773 | Journal Article (Survey paper) | Scientific

Scopus - Urology SJR indicator: **D1**

Scopus - Cancer Research SJR indicator: Q1

Scopus - Oncology SJR indicator: Q1

IF: 5.1

16.2. Publications not related to the thesis

1. Matsukawa A., Yanagisawa T., Parizi M.K., Laukhtina E., Klemm J., **Fazekas T**., Mori K., Kimura S., Briganti A., Ploussard G., Karakiewicz P.I., Miki J., Kimura T., Rajwa P., Shariat S.F.

Cardiovascular events among men with prostate cancer treated with androgen receptor signaling inhibitors: a systematic review, meta-analysis, and network meta-analysis

PROSTATE CANCER AND PROSTATIC DISEASES 28: 2 pp. 298-308., 11 p. (2025)

Publication: 35333578 | Journal Article (Survey paper) | Scientific

Scopus - Urology SJR indicator: D1

Scopus - Cancer Research SJR indicator: Q1

Scopus - Oncology SJR indicator: Q1

IF: 5,8

2. Matsukawa A., Yanagisawa T., Rajwa P., **Fazekas T**., Miszczyk M., Tsuboi I., Parizi M.K., Laukhtina E., Klemm J., Chiujdea S., Mancon S., Mori K., Kimura S., Karakiewicz P.I., Miki J., Kimura T., Shariat S.F.

Central Nervous System Toxicity in Prostate Cancer Patients Treated with Androgen Receptor Signaling Inhibitors: A Systematic Review, Meta-analysis, and Network Meta-analysis

CLINICAL GENITOURINARY CANCER 23: 1 Paper: 102251, 11 p. (2025)

Publication: 35598193 | Journal Article (Survey paper) | Scientific

Scopus - Urology SJR indicator: Q1

Scopus - Oncology SJR indicator: Q2

IF: 2,7

3. Schulz, R.J.; Ofner, H.; Nyirády, P.; Rajwa, P.; Weiss, J.; Shariat, S.F.; **Fazekas, T.**

Overlooked and underserved: how healthcare fails men in the pursuit of equity

CURRENT OPINION IN UROLOGY 35: 2 pp. 148-156., 9 p. (2025)
Publication: 35700411 | Journal Article (Survey paper) | Scientific
Scopus - Urology SJR indicator: Q2
IF: 2,2

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IF: 4,5

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Scopus - Medicine (miscellaneous) Rank: D1
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Scopus - Medicine (miscellaneous) Rank: D1
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