Population

Describe the population in which the proposed health technology is intended to be used:
Adult patients with metastatic castration-resistant prostate cancer (mCRPC) with evidence of BReast CAncer (BRCA) gene 1 or BRCA 2 gene alteration

Additional information

Prostate cancer is one of the major health issues of elderly men in the word. Although the prognosis of prostate cancer is generally good, an estimated 10% to 20% of patients progress to castration-resistant disease within a 5-year period (Kirby 2011). Castration-resistant prostate cancer (CRPC) is an advanced form of the disease characterised by continued progression despite maintaining serum testosterone at castrate levels (<50 ng/dL) (Parker 2020, NCCN Guidelines 2022). Most patients develop mCRPC following progression from earlier stages of the disease, with an estimated 65% to 72.6% progressing to mCRPC from metastatic castration sensitive prostate cancer (mCSPC), and 26.2% to 35% progressing from non-metastatic castration-resistant prostate cancer (nmCRPC) (Shore 2021, Lam 2018).

Bone is the predominant site of metastasis in prostate cancer (Kirby 2011) and more than 84% of patients have bone metastases at diagnosis of mCRPC. Other common sites of metastasis in patients with mCRPC include lung and liver (Halabi 2016). mCRPC is generally associated with the poorest prognosis, with recent real-world studies reporting median survival of less than 4 years (Francini 2019, Chowdhury 2020, Westgeest 2021).

Prostate cancer growth and proliferation are primarily dependent on androgens, and androgen deprivation therapy (ADT) is an effective means of controlling the disease. However, some men develop resistance to androgen deprivation, resulting in the development of castration-resistant prostate cancer (CRPC).

Established risk factors for prostate cancer include, but are not limited to, advanced age, family history of disease, certain genetic mutations (e.g., BRCA1/2), Lynch Syndrome and African American descent (Parker 2020). Environment and lifestyle factors such as, smoking, excess body weight, nutritional factors, excess multivitamin use, and dairy and calcium intake, have also been recognized to increase the risk of prostate cancer (NCCN Guidelines 2022).

Early-stage prostate cancer is often asymptomatic. Patients with more advanced cases of prostate cancer can experience symptoms including difficulty urinating, blood in urine or semen, erectile dysfunction, weakness or numbness in legs or feet, and pain in the hips, spine, ribs or other areas where cancer has spread to bone. Compared to the non-metastatic disease stage, patients who progress to mCRPC tend to report greater symptom burden, including fatigue, pain, and urinary frequency and more deterioration in functional well-being (Holmstrom et al, 2019). Because metastasis is predominantly localised in bones (90% of patients with mCRPC), this causes significant morbidity which requires medical interventions (pain and skeletal-related events, spinal cord compression, pathological fractures, etc) (Gandaglia et al, 2015).

Inherited mutations in several genes involved in DNA damage repair have been reported to predispose men to prostate cancer. Between 24% to 30% of mCRPCs have loss of function mutations in genes involved in homologous recombination repair (HRR) of DNA damage response (DDR) (Abida, 2017, Armenia, 2018, Chung, 2019). Mutations in the breast cancer susceptibility genes (BRCA1and/or BRCA2) are the most prevalent HRR gene mutations in mCRPC (with BRCA2 more prevalent than BRCA1) Abida, 2017, Armenia, 2018, Chung, 2019)

Prostate cancer is a significant cause of morbidity and mortality in men, especially in those over the age of 75 years and impacts their physical, emotional and social life (National Institute for Health Research, April 2019). Data obtained from AIHW 'Cancer Data in Australia' in 2022 estimated that 24,217 new cases of prostate cancer were diagnosed, and thus likely to be the most commonly diagnosed cancer in males. In 2022, it is estimated that a male has a 1 in 6 (or 17%) risk of being diagnosed with prostate cancer by the age of 85. In 2022, the age-standardised incidence rate was estimated to be 150.8 cases per 100,000 males (AIHW 2022).

In 2020, prostate cancer was the third most common cause of cancer death in Australia. The mortality rate was 232 deaths per 100,000 males. Approximately 88% of prostate cancer deaths occurred in the male population aged over 70 years. The number of deaths from prostate cancer (all ages) was 3,568 deaths (with 3,138 deaths for males aged over 70) in 2020. The increase in ageing population will impact prostate cancer mortality statistics. This is because the increase in the number of men reaching higher risk ages for prostate cancer is likely to lead to an increasing number of deaths from prostate cancer in the future (AIHW 2022). In 2022, it is estimated that prostate cancer will become the fourth most common cause of death from cancer, with an estimated 3,507 deaths from this disease.

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

The proposed amendment is related to the medical service for testing of tumour prostate tissue to detect BRCA1/2 gene mutations in men with metastatic castration resistant prostate cancer (mCRPC) to include treatment with talazoparib. Many patients with mCRPC are currently undergoing genetic testing to determine their eligibility for PBS-listed olaparib monotherapy.

Prostate cancers are often discovered early through routine screenings. For early detection and screening in patients without symptoms, prostate-specific antigen (PSA) testing and digital rectal exams (DRE) are recommended. If abnormal DRE results or elevated PSA levels are present, biopsies are typically necessary to provide a definitive diagnosis (NCCN Guidelines 2022). Biopsy testing is required for a definitive diagnosis of prostate cancer. As a first-line investigation for patients with suspected prostate cancer, multiparametric magnetic resonance imaging (mpMRI) is recommended to confirm need for biopsy (NICE 2019). The following step after a positive mpMRI is a systematic prostate biopsy, such as a transrectal ultrasonography biopsy. Therefore, some of the routine tests that may be performed to investigate symptoms of prostate cancer and confirm a diagnosis include (Australian Government, Cancer Australia, 2017):

- physical examination and medical history
- digital rectal examination
- blood test to check for prostate-specific antigen (PSA), a protein produced by the prostate. The level of PSA can be higher than normal in people with prostate cancer (but also in people with other prostate conditions that are not cancer)
- transrectal ultrasound – where a probe is inserted into the rectum that uses sound waves to create a picture of the prostate inside the body
- magnetic resonance imaging (MRI)
- biopsy – where a small sample of tissue is removed to be examined under a microscope. The biopsy results include a Gleason score – a score from 2 to 10 used by the pathologist that indicates the likelihood of the tumour spreading outside the prostate (2 is least likely to spread, and 10 is most likely to spread).

Following diagnosis, tests to determine the stage of prostate cancer can include (Australian Government, Cancer Australia, 2017):

- transrectal ultrasound
- biopsy or removal of lymph nodes – where tissue from the lymph nodes is taken to be examined under a microscope
- bone scan
- CT, MRI or other scans

Localised stage prostate cancer can be cured with surgery or radiotherapy, but some patients will relapse with either overt metastases or an isolated rise in PSA. A proportion of these patients are found to have a local relapse and can have salvage therapy (generally radiation), but the remainder of cases are considered to have incurable advanced disease. There is also a proportion of men who have metastases when the prostate cancer is first diagnosed.

For patients who have already been diagnosed with prostate cancer, serial PSA testing, repeat biopsies, and MRI scans may be used to monitor patients for disease progression (Parker et al, 2020). These procedures are also used to monitor for disease recurrence in patients following radical treatment for prostate cancer. CRPC is diagnosed based on disease progression despite maintaining castration levels of testosterone. Imaging tests such as MRI scan, computed tomography (CT) scans or isotope bone scans are used to detect potential spread of the cancer, including to distant sites such as bone (NICE 2019). If there is evidence of metastasis, the disease state is defined as metastatic prostate cancer. The management of advanced and metastatic disease is predominantly medical. While the cancer is incurable, it is not untreatable.

Only a small proportion of patients with mCRPC have loss of function mutations in candidate genes involved in homologous recombination repair (HRR) of DNA. BRCA1 and BRCA2 are the most well characterised. During its consideration of olaparib's co-dependent submission as a monotherapy for mCRPC patients with BRCA1/2 mutations, MSAC advised that the prevalence estimates of BRCA1/2 in the Australian population with mCRPC and BRCA1/2 pathogenic variants ranges between 7%–10% (p4, MSAC 1618, PSD, March 2021). The PBAC considered that the lower end of this range (7%) is more appropriate as rates of BRCA1/2 prevalence appear lower in practice than reported in the literature (Table 2, olaparib PSD, November 2021). This prevalence rate was calculated based on the number of patients tested and the proportion of tests that was positive for BRCA1/2 pathogenic variants from the olaparib trial (PROfound) (Clause 4.4, olaparib PSD, November 2021). In TALZENNA pivotal TALAPRO-2 trial (Cohort 1 - all comers population), there were 60 patients that were BRCA1/2 positive, equivalent to a prevalence of 7.4%, and consistent with PBAC's 7% prevalence for BRCA1/2 pathogenic variants in the Australian population.

In Australia, the eviQ consensus statement for prostate cancer panel testing recommend BRCA testing in patients with prostate cancer and ≥ 10% probability of detecting a BRCA1 or BRCA2 gene variant using a validated pathogenic variant prediction tool i.e. a pathogenic variant already identified in the patient's family (see Q. 27 for further details).

Provide a rationale for the specifics of the eligible population:
The proposed amendment is related to the medical service for testing of germline or tumour prostate tissue to detect BRCA1/2 gene mutations in men with mCRPC to include treatment with talazoparib. Many patients with mCRPC are currently undergoing genetic testing to determine their eligibility for PBS-listed olaparib monotherapy.

The pivotal TALAPRO-2 RCT of talazoparib plus enzalutamide in mCRPC presents clinical data for three populations: 1) Cohort 1 – intention-to-treat (ITT) all-comers population; 2) Cohort 2 – ITT

selected for homologous recombination repair (HRR) deficiencies and 3) prespecified BRCA1/2 subpopulation from Cohort 2 which accounted for 39.6% of the overall population of Cohort 2 (HRR deficient population). All patients in Cohort 2 were prospectively tested for genomic alterations in 12 HRR genes (BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12). Patients were considered HRR-deficient if they had at least 1 mutation in 1 or more of the 12 genes described or if there was a discordant result between the tissue and liquid result.

The clinical study report (CSR Cohort 1) for the Phase III TALAPRO-2 trial for talazoparib, Section 3.5 (Study Assessments and Procedures) includes a detailed description BRCA testing that occurred in the pivotal trial. It states that "*the assessment of HRR mutation status (a panel of 12 genes that included BRCA1 & BRCA2) by prospective analysis was performed via de novo or archival tissue or historical analysis (with sponsor approval) using FoundationOneCDx (tissue). Participants were considered HRR-deficient if the participant had at least 1 mutation in 1 or more of the 12 genes (described in first Table in Section 3.5.2) or if there was a discordant result between the tissue and liquid result. If prospective results from blood and tumor tissue samples were both available, a positive result from either was considered prospectively DDR deficient.*" (CSR TALAPRO-2, Section 3.5.2).

It should be noted that the streamlined co-dependent submission the was lodged on 01 November 2023 via the HPP requested the PBS-listing of talazoparib (to be used in combination with PBS listed enzalutamide) for the treatment of mCRPC patients who have evidence of a BRCA1/2 gene mutation only.

Are there any prerequisite tests?
Yes

Are the prerequisite tests MBS funded?
Yes

Please provide details to fund the prerequisite tests:
N/A

Intervention

Name of the proposed health technology:
Germline and tumour (somatic) BRCA1/2 mutation testing is currently performed in Australia under MBS item numbers 73303 and 73304 to determine mCRPC patients' eligibility for treatment with olaparib monotherapy on the PBS. Therefore, this application requests amending MBS items 73303 and 73304 to include treatment with talazoparib.

Describe the key components and clinical steps involved in delivering the proposed health technology:
BRCAm may be either germline, meaning the mutation originated in the germ cells of a parent and was inherited, or somatic. Somatic mutations may occur at any time after conception in any of the cells of the body except for germ cells. Since April 2022, patients with mCRPC have access to MBS funded genetic testing to detect both somatic and/or germline BRCA1 or BRCA2 gene variants, to determine eligibility for the PBS listed olaparib monotherapy.

The eviQ consensus statement for prostate cancer panel testing recommend BRCA testing in patients with prostate cancer and ≥ 10% probability of detecting a BRCA1 or BRCA2 pathogenic variant using a validated pathogenic variant prediction tool i.e. a pathogenic variant already identified in the patient's family. This includes patients with:

- Prostate cancer where a pathogenic variant in a gene listed below has been detected on tumour testing.
- Castrate-resistant metastatic prostate cancer (regardless of other personal or family history factors) for whom genetic testing on tumour DNA is not clinically feasible.
- Prostate cancer and ≥ 10% probability of detecting a BRCA1 or BRCA2 pathogenic variant using a validated pathogenic variant prediction tool (e.g. CanRisk).
- Prostate cancer with intraductal/ductal histology.
- Prostate cancer from a population where a founder pathogenic variant of high prevalence exists (e.g. Ashkenazi Jewish, Swedish/Nordic).

The current key components and clinical steps involved in delivering a tumour BRCA mutation test are as follows:

1. Patient's tumour sample is taken and sent to a pathology laboratory where BRCA testing is performed. Tumour tissue specimens for BRCA testing may be obtained as either a fresh tissue or an archived tissue specimen as formalin-fixed paraffin-embedded (FFPE) blocks, following primary tumour debulking surgery. DNA is extracted, purified and quantified using the laboratory's preferred commercially available kits. PCR amplification methods may be used. Libraries for sequencing are prepared and library quality may be evaluated at this step. Some gene panels (e.g. BROCA) identify all classes of mutations including single base substitutions, small insertions and deletions and large gene re-arrangements. Variants are called using comparison to reference libraries. Next-generation sequencing is performed and sequencing results are then reported to the requesting specialist or consultant physician. Tumour tissue specimens obtained as FFPE blocks may have been archived for many months or years prior to tumour testing. Retrieval of archived samples may add up to 2 weeks to the turnaround time for the test, and preparation, extraction and then interpretation can add several additional weeks. It is likely that specialists and consultants may prefer to obtain new tissue samples. However, in some circumstances (such as a long period in archive or issues with the FFPE

process) there may be degradation of the DNA in the specimen and a re-biopsy may be necessary. A fresh biopsy may also be required in cases where initial neo-adjuvant chemotherapy resulted in significant tumour shrinkage and tumour debulking surgery did not provide any viable tumour tissue. Costs ($88 for block retrieval) will be incurred for retrieving samples from archive and possibly for forwarding them on to the specialist molecular diagnostic laboratories who are able to analyse the tissue. There may be additional harms to patient due to the need for re-biopsy in some cases.

2. The results are sent to the treating medical practitioner. If a mutation is detected, a face-to-face post-test counselling appointment with the patient and their family is arranged to deliver the results. Individuals identified as harbouring a pathogenic mutation (Class 4 or 5) are referred to Genetics Services/Familial Cancer Centres for post-test counselling. Patients with a VUS or strong family history should also be referred for post-test counselling.
3. Based on a positive mutation for BRCA, the medical practitioner will consider prescribing talazoparib to the patient if they meet the PBS criteria to access treatment

Identify how the proposed technology achieves the intended patient outcomes:
Genetic testing for patients with mCRPC has the potential to improve outcomes by identifying hereditary mutations such as BRCA1/2 in patients leading to better treatment options and outcomes. As described below, results from the pivotal Phase III TALAPRO-2 randomised controlled trial evaluating TAL + ENZ versus placebo (PBO) + ENZ in patients with mCRPC has demonstrated that the first-line (1L) treatment with TAL + ENZ provides statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS) while maintaining QoL. Prespecified subgroup analyses from the trial demonstrated that the greatest benefits in rPFS and overall survival (OS) are observed in patients with BRCA1/2 gene mutations.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
No

The test does not have a registered trademark. However, registered trademarks may be held by the various commercial kits used at the different stages of the testing process (e.g. DNA extraction, quality assurance, quantification, PCR amplification, Next Generation Sequencing [NGS] platform).

The medicine talazoparib (brand name TALZENNA®) is a registered trademark.

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient?:
No

Provide details and explain:
It is unlikely that a patient would require more than one tumour BRCA1/2 test in their lifetime.

BRCA testing is well established in Australia and is currently performed in mCRPC, as well as in breast and ovarian cancer. It is performed by many accredited public and private pathology laboratories in Australia.

If applicable, advise which health professionals will be needed to provide the proposed health technology:
Testing to identify BRCA1/2 gene mutations should be conducted and the results interpreted and reported by suitably qualified and trained molecular pathologists. Testing should be conducted in specialist laboratories holding the appropriate accreditation.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
Addressed above

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
Yes

Provide details and explain:
Testing to identify BRCA1/2 gene mutations in patients with mCRPC should be based on a referral request from a specialist or consultant physician and should not be pathologist determinable.

All laboratories that perform BRCA testing are accredited to the Royal College of Pathologist of Australasia (RCPA) Quality Assurance Programs. For further information please refer to the website: https://www.rcpaqap.com.au/home-page

Indicate the proposed setting(s) in which the proposed health technology will be delivered: (select all relevant settings)
- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Emergency Department
- ☐ Inpatient private hospital
- ☐ Inpatient public hospital
- ☒ Laboratory
- ☐ Outpatient clinic
- ☐ Patient's home
- ☐ Point of care testing
- ☐ Residential aged care facility
- ☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?
Yes

Please provide additional details on the proposed health technology to be rendered outside of Australia:
N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:
The nominated comparator in the PBAC submission is enzalutamide monotherapy. Enzalutamide and abiraterone monotherapy are PBS listed and are standard of care for 1L treatment of mCRPC in Australia.

List any existing MBS item numbers that are relevant for the nominated comparators:
BRCA1/2 somatic or germline mutation testing is currently performed in mCRPC to determine eligibility for PBS-listed olaparib (MBS item numbers 73303 and 73304). No genetic testing is required for enzalutamide (or abiraterone) for the 1L treatment of mCRPC.

Please provide a rationale for why this is a comparator:
As stated above, enzalutamide monotherapy is PBS listed and is standard of care for 1L treatment of mCRPC in Australia. Talazoparib is an add-on therapy to enzalutamide and the requested PBS listing is for mCRPC patients with a BRCA1/2 mutation. BRCA1/2 mutation testing in mCRPC is performed to access PBS listed olaparib which is a 'subsequent" line of therapy in mCRPC.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

☒ None *(used with the comparator)*
☐ Displaced *(comparator will likely be used following the proposed technology in some patients)*
☐ Partial *(in some cases, the proposed technology will replace the use of the comparator, but not in all cases)*
☐ Full *(subjects who receive the proposed intervention will not receive the comparator)*

Please outline and explain the extent to which the current comparator is expected to be substituted:
As discussed above, the current MBS items 73303 and 73304 for BRCA1/2 mutation testing are not expected to be substituted. BRCA1/2 mutation testing in mCRPC to determine eligibility for PBS-listed olaparib is expected to continue to be performed in the future, and the listing of talazoparib on the PBS will not alter the utilisation of this service.

Outcomes

(Please copy the below questions and complete for each outcome)

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☐ Resources
☐ Value of knowing

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Newly diagnosed mCRPC patients who have evidence of BRCA1/2 gene mutations, and who have not received prior novel hormonal agent, will be eligible to receive the combination therapy of TAL + ENZ. For patients who have progressed on the combination of TAL + ENZ in the first-line setting will not be eligible to receive olaparib monotherapy in second or subsequent lines. Further, prostate cancer patients who are receiving treatment with an NHA (darolutamide, apalutamide or enzalutamide) for mHSPC or nmCRPC will not be eligible to receive TAL + ENZ combination therapy if their disease progresses to mCRPC (and are BRCA1/2 positive), consistent with the current PBS restriction relating to only one NHA once in a lifetime.

Proposed MBS items

How is the technology/service funded at present? (for example: research funding; State-based funding; self-funded by patients; no funding or payments):

MBS funded.

This application seeks an amendment to MBS Item 73303 and MBS item 73304 to add access to talazoparib (a PARP inhibitor) under the Pharmaceutical Benefits Scheme. The change will not result in a change to testing methodology, the patient population who access testing through the MBS, or to the MBS fee.

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention: (please copy the below questions and complete for each proposed item)

MBS item number	73303
Category number	6
Category description	PATHOLOGY SERVICES
Proposed item descriptor	A test of tumour tissue from a patient with metastatic castration-resistant prostate cancer, including subsequent characterisation of germline gene variants should tumour tissue testing undertaken during the same service be inconclusive, requested by a specialist or consultant physician, to determine eligibility relating to BRCA status for access to olaparib ***or talazoparib*** under the Pharmaceutical Benefits Scheme. Applicable once per primary tumour diagnosis
Proposed MBS fee	$1,000
Indicate the overall cost per patient of providing the proposed health technology	$1,000
Please specify any anticipated out of pocket expenses	$250
Provide any further details and explain	Applicable once per lifetime Proposed additions are italicised in table. The change will not result in a change to testing methodology, the patient population who access testing through the MBS, or to the MBS fee

MBS item number	73304
Category number	6
Category description	PATHOLOGY SERVICES
Proposed item descriptor	Detection of germline BRCA1 or BRCA2 pathogenic or likely pathogenic gene variants, in a patient with metastatic castration-resistant prostate cancer, for whom testing of tumour tissue is not clinically feasible, requested by a specialist or consultant physician, to determine eligibility for olaparib ***or talazoparib*** under the Pharmaceutical Benefits Scheme.
Proposed MBS fee	$1,000
Indicate the overall cost per patient of providing the proposed health technology	$1,000
Please specify any anticipated out of pocket expenses	$250
Provide any further details and explain	Applicable once per lifetime Proposed additions are italicised in table. The change will not result in a change to testing methodology, the patient population who access testing through the MBS, or to the MBS fee.

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:
In Australia, enzalutamide and abiraterone (as monotherapy) are the standard of care for 1L mCRPC. A small proportion (<10%) of mCRPC patients may receive docetaxel initially to slow the growth of cancer cells before initiating therapy with novel hormonal agent (NHA), however, docetaxel's main place in the treatment algorithm is post-progression on an NHA. In the second-line setting, olaparib is listed on the PBS as a monotherapy for patients with BRCA1/2 gene mutations following progression on NHA in first line (mCRPC, non-metastatic CRPC or metastatic hormone sensitive prostate cancer [mHSPC]). For patients who do not have BRCA1/2 gene mutations, docetaxel remains the preferred treatment option post progression on NHA. Cabazitaxel is the recommended treatment of mCRPC after docetaxel failure. Figure 1 below presents the current treatment algorithm for mCRPC in the Australian setting. The treatment algorithm also accounts for patients who are treated with NHAs (darolutamide, apalutamide or enzalutamide) in the nmCRPC and mHSPC settings.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No.

BRCA1/2 mutation testing in mCRPC is not expected to change as a result of talazoparib listing on the PBS, because it is required to access to olaparib monotherapy on the PBS.

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
N/A

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:
Same healthcare resources as per BRCA1/2 testing performed to access PBS-listed olaparib.

Explain what other healthcare resources are used in conjunction with the comparator health technology:
N/A

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:
N/A

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:
The proposed treatment algorithm is presented in Figure 2 and shows the place of TAL + ENZ if listed on the PBS. Patients diagnosed with mCRPC and without a BRCA1/2 gene mutation will continue to be treated as per current treatment algorithm shown in Figure 1. Those mCRPC patients who have evidence of BRCA1/2 gene mutations, and who have not received prior NHA, will be eligible to receive the combination therapy of TAL + ENZ. For patients who have progressed on the combination of TAL + ENZ in the first-line setting will not be eligible to receive olaparib monotherapy in second or subsequent lines. Further, prevalent patients who are receiving treatment with an NHA (darolutamide, apalutamide or enzalutamide) for mHSPC or nmCRPC will not be eligible to receive TAL + ENZ combination therapy if their disease progresses to mCRPC (and are BRCA1/2 positive), consistent with the current PBS restriction relating to only one NHA once in a lifetime.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:
N/A

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:
N/A

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

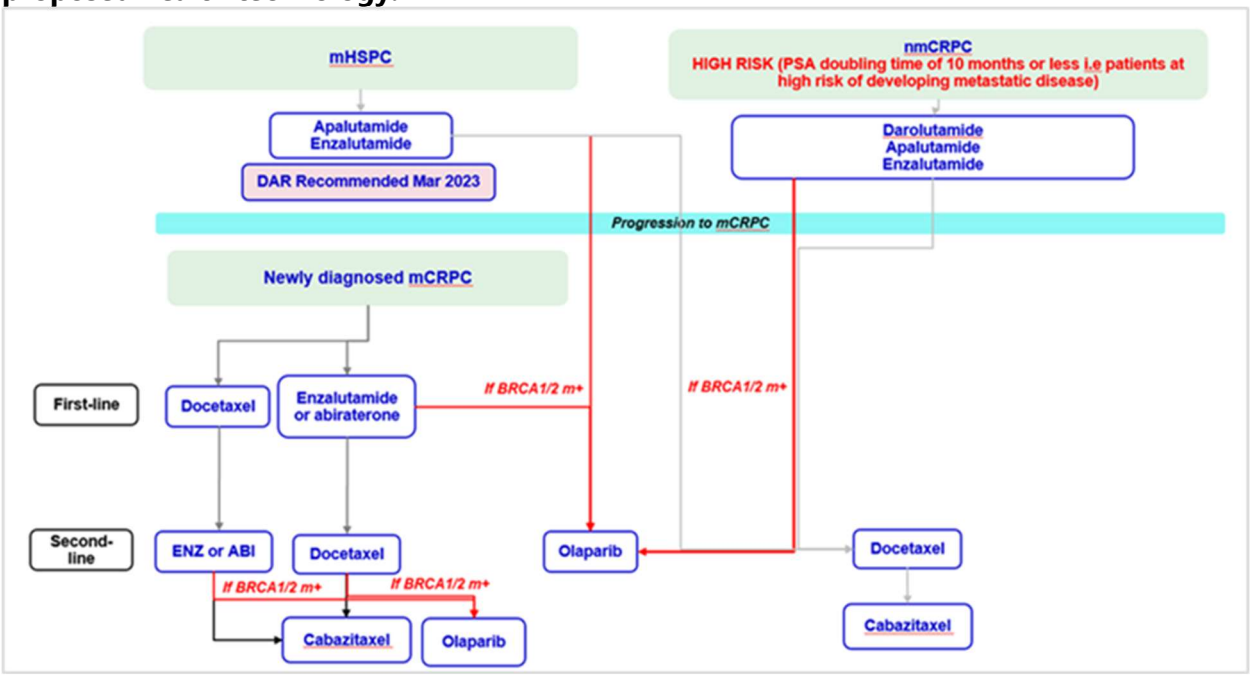


Figure 1 Current treatment algorithm

Abbreviations: ABI, abiraterone; BRCA, BReast CAncer gene; DAR, darolutamide; ENZ, enzalutamide; HSPC, hormone sensitive prostate cancer nmCRPC, non-metastatic castration resistant prostate cancer; mCRPC, metastatic castration resistant prostate cancer.

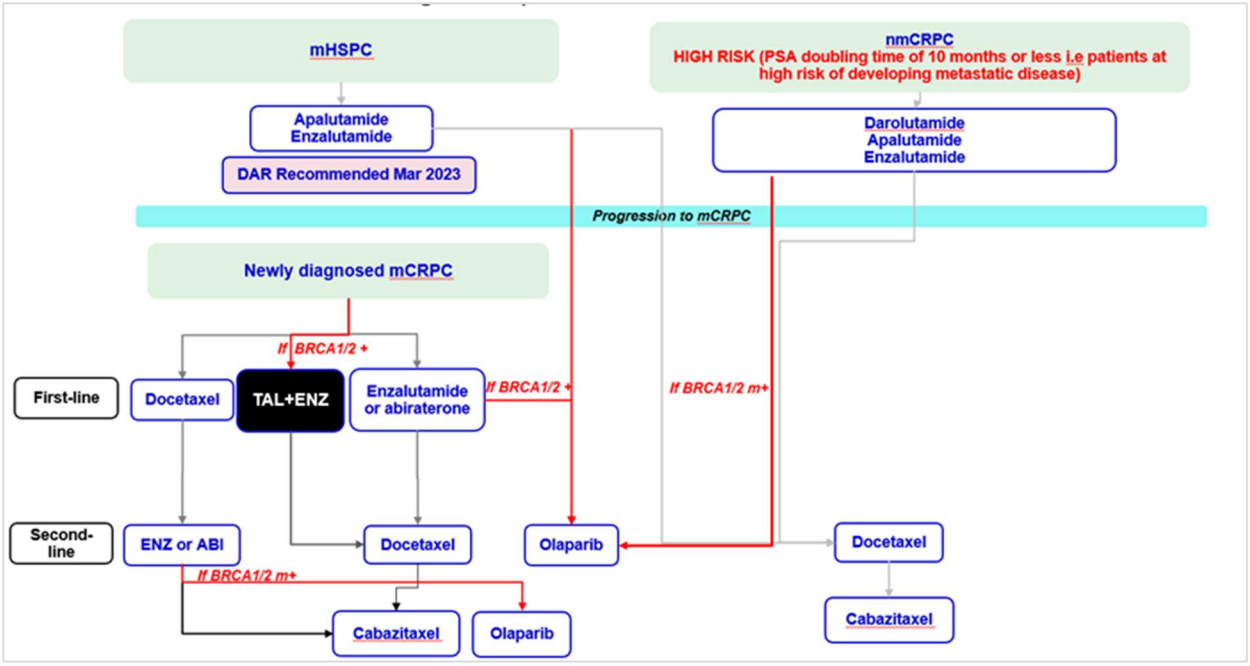


Figure 2 Proposed treatment algorithm

Abbreviations: ABI, abiraterone; BRCA, BReast CAncer gene; DAR, darolutamide; ENZ, enzalutamide; HSPC, hormone sensitive prostate cancer nmCRPC, non-metastatic castration resistant prostate cancer; mCRPC, metastatic castration resistant prostate cancer

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☒ Superior
☒ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

Efficacy:
A clinical claim of superior efficacy is made for TAL+ENZ versus PBO + ENZ.

Safety:

TAL + ENZ has an inferior safety profile to PBO + ENZ, with this being regarded as tolerable and manageable, as evidenced by no detriment to QoL.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
The proposed population in the PBAC submission for talazoparib is mCRPC with BRCA1/2 gene mutations. Therefore, genetic testing that is currently performed in the mCRPC patients with identify patients eligible for treatment with talazoparib.

Identify how the proposed technology achieves the intended patient outcomes:
The clinical evidence informing the comparative efficacy of TAL+ENZ vs ENZ is derived from the pivotal Phase III TALAPRO-2 RCT that compared TAL+ENZ with PBO+ENZ in mCRPC patients with BRCA1/2 gene mutations. The evidence presented is supportive of a clinical claim of superior efficacy and-inferior but manageable safety profile for TAL + ENZ versus PBO + ENZ.

TALAPRO-2 is a Phase III, double-blind RCT that evaluated the efficacy and safety of TAL + ENZ in patients with mCRPC in two cohorts with equally split alpha for data analysis: unselected (Cohort 1, the allcomers cohort, recruited first) and selected (Cohort 2, HRR-deficient only, which completed recruitment after completion of enrolment in Cohort 1) for DNA damage response alterations in genes directly or indirectly involved in HRR. The study prospectively assessed the HRR gene alteration status in tumour tissue, considered a gold standard for establishing the biomarker status in cancer. Furthermore, the study used HRR status (HRR positive vs HRR negative or unknown status) as a prespecified stratification factor to establish benefits in each group. Testing for genomic alterations included 12 HRR genes: BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12. 805 patients were enrolled in Cohort 1, of which, 636(79.0%) were non-HRR-deficient or had unknown HRR status and 169 (21.0%) were HRR-deficient). Cohort 2 included the 169 patients from Cohort 1 who were HRR-deficient as well as an additional 230 patients enrolled directly into the cohort, for a total of 399 patients.

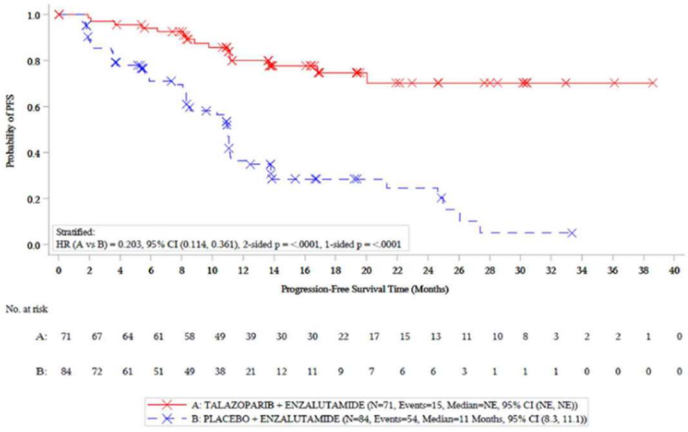
Patients were randomized 1:1 to receive 0.5 mg/day TAL or matched placebo in combination with 160 mg/day ENZ. The primary endpoints were rPFS per blinded independent central review (BICR) in Cohort 1 and Cohort 2. The key secondary endpoint is OS (alpha protected). The trial was powered to detect significant improvement in rPFS in both of its populations. The prespecified subgroup analyses for BRCA1/2 gene alteration indicate that the greatest improvement in the primary endpoint of rPFS and the key secondary endpoint of OS has been demonstrated for patients with BRCA1/2 genetic alteration (39.6% of patients enrolled in Cohort 2).

A summary of the final results of rPFS assessed by BICR for all randomised patients from Cohort-2 (ITT HRR deficient) and for the subgroup of patients with BRCA1/2 gene mutation is presented in Table 1. Importantly, subgroup analyses of rPFS for patients with BRCA1/2 assigned to TAL + ENZ had a statistically significant and clinically meaningful improvement in rPFS compared with BRCA1/2 patients assigned to PBO + ENZ (HR 0.20; 95%CI: 0.11, 0.36; p-value <0.0001). The median rPFS was not reached (NR) in the TAL + ENZ arm and was 11.0 months in the PBO + ENZ arm.

Table 1 Summary of rPFS based on BICR assessment – Cohort 2 (ITT patients selected for HRR deficiencies), BRCA1/2 and non-BRCA1/2 subgroup populations

	Cohort 2- ITT HRR def		Cohort 2 – BRCA1/2		Cohort 2 – non-BRCA1/2	
	TAL + ENZ N=200	PBO + ENZ N=199	TAL + ENZ N=71	PBO + ENZ N=84	TAL + ENZ N=127	PBO + ENZ N=113
rPFS - BICR (IA 03 October 2022)						
Events, n (%	66 (33.0)	104 (52.3)	15 (21.1)	54 (64.3)	50 (39.4)	50 (44.2)
Median (95% CI), months	NR (21.9, NR)	13.8 (11.0, 16.7)	NR (NR, NR)	11.0 (8.3, 11.1)	24.7 (16.4, NR)	16.7 (13.8, 27.7)
HR (95% CI)	0.45 (0.33, 0.61)		0.20 (0.11, 0.36)		0.69 (0.46, 1.02)	
One sided p-value	< 0.0001		< 0.0001		0.0298	

BRCA1/2 03 OCT 2022 datacut



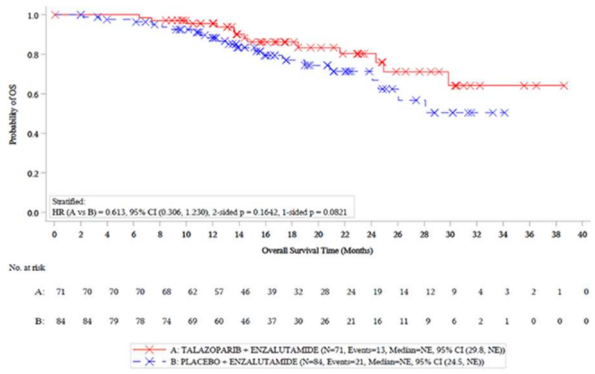
Source: Section 2.5 and Section 2.6.1. Abbreviations: BICR, blinded independent central review; CI, confidence interval; ENZ, enzalutamide; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; NR, not reached; rPFS, radiographic progression-free survival; TAL, talazoparib.
For K-M estimates, CIs are calculated using Brookmeyer and Crowley method.
For HR and 1-sided p-value estimates, a Cox proportional hazard model and a stratified log-rank test were used, respectively.

A summary of the efficacy results of OS for patients with HRR deficiencies and for the subgroup of patients with BRCA1/2 gene alteration is presented in Table 2. **Error! Reference source not found.**These analyses are from the IA 03 October 2022. An updated analysis for OS from the 28 March 2023 data cutoff is presented in the PBAC submission for talazoparib but only for the patients with BRCA1/2 gene alterations. As stated above, rPFS results from the IA 03 October 2022 were final and no updated rPFS analysis is available from the 28 March 2023 data cutoff.

As of the 03 October 2022 data cutoff, 34 death events were observed (22% data maturity) in patients with BRCA1/2 gene alterations, of which 13 occurred in the TAL + ENZ arm and 21 occurred in the PBO + ENZ arm. At this IA, OS analysis showed a trend in favour of TAL + ENZ with the observed stratified HR of 0.61 (95% CI: 0.31 to 1.23; p=0.0821) for TAL + ENZ versus PBO + ENZ. Median OS was not reached (95% CI: 29.8 to NR) in the TAL + ENZ arm and was also not reached (95% CI: 24.5 to NR) in the PBO + ENZ arm. Median OS was also immature for patients with HRR deficiencies (ITT) and the subgroup of patients without BRCA alterations.

Table 2 Summary of OS –Cohort 2 (ITT selected for HRR deficiencies), BRCA1/2 & non-BRCA1/2 subgroup populations.

	Cohort 2- ITT HRR deficient		Cohort 2 – BRCA1/2		Cohort 2 – non-BRCA1/2	
OS	**TAL + ENZ N=200**	**PBO + ENZ N=199**	**TAL + ENZ N=71**	**PBO + ENZ N=84**	**TAL + ENZ N=127**	**PBO + ENZ N=113**
IA 03 October 2022						
Events, n (%)	43 (21.5)	53 (26.6)	13 (18.3)	21 (25.0)	29 (22.8)	32 (28.3)
Median (95% CI), months	NR (36.4, NR)	33.7 (27.6, NR)	NR (29.8, NR)	NR (24.5, NR)	36.4 (36.4, NR)	33.7 (27.6, NR)
HR (95% CI)	0.69 (0.46, 1.03)		0.613 (0.306, 1.230)		0.664 (0.399, 1.105)	
One sided p-value	0.0338		0.0821		0.0560	
A. BRCA1/2 (03 OCT 2022 datacut)						



Source: TALAPRO-2 Cohort 2 CSR_ Section 2.5 and Section 2.6.1. Abbreviations: CI, confidence interval; ENZ, enzalutamide; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; NE, not evaluable; NR, not reached; OS, overall survival; TAL, talazoparib. For K-M estimates, CIs are calculated using Brookmeyer and Crowley method. For HR and 1-sided p-value estimates, a Cox proportional hazard model and a stratified log-rank test were used, respectively.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits? No

Please provide a rationale, and information on other benefits if relevant:

Safety results (required to support the claim of non-inferiority in terms of safety)

The summary of safety outcomes in the safety population for Cohort-2 (ITT HRR deficient population) is presented in Table 3. Overall, the incidence of TEAEs of any grade was higher for TAL + ENZ vs PBO + ENZ (99.0% versus 96.0%). Treatment-related AEs were reported in 90.9% of patients in the TAL + ENZ group and in 72.4% of patients in the PBO + ENZ group. The frequency of grade 3/4 TEAE also occurred in a higher proportion of patients in the TAL + ENZ group than in the PBO + ENZ group (66.2% and 37.2%, respectively). Grade 5 TEAEs occurred in 1.5% of patients

in the TAL + ENZ group and in 2.5% of patients in the PBO + ENZ group. No (fatal) grade 5 treatment-related AEs occurred in the TAL + ENZ group or the PBO + ENZ group. There were no cases of myelodysplastic syndrome or acute myeloid leukemia during the safety reporting period or the follow-up period in the TAL + ENZ or PBO + ENZ group. Pulmonary embolism was reported in 2.0% of patients (n=4; grade ≥3 in 3 patients) in the TAL + ENZ group and in 1.0% (n=2; grade ≥3 in 2 patients) in the PBO + ENZ group.

Table 3 Summary of adverse events (Cohort 2 – ITT HRR deficient population)

Adverse events, n (%)	TAL + ENZ N = 198	PBO + ENZ N = 199
Any adverse event	182 (91.9)	111 (56.1)
Serious TEAE	60 (30.3)	40 (20.1)
TEAE grade 3 or 4, n (%)	131 (66.2)	74 (37.2)
Grade 5 TEAE	3 (1.5)	5 (2.5)

Source: TALAPRO-2 CSR Cohort 2 Section 5.2.1. Adverse Events, Table 27 and Table 28
Abbreviations: AE, adverse event; CI, confidence interval; ENZ, enzalutamide; PBO, placebo; TAL, talazoparib; TEAE, treatment emergent adverse event.

In Cohort 2, 10.1% of patients in the TAL + ENZ group and 7.6% of patients in the PBO + ENZ group experienced AEs leading to discontinuation of TAL or PBO. AEs leading to dose interruption of TAL were reported in 57.6% of patients in the TAL + ENZ group and AEs leading to dose interruption of PBO were reported in 17.1% of patients in the PBO + ENZ group. AEs leading to dose reduction of TAL were reported in 52.0% of patients in the TAL + ENZ group and AEs leading to dose reduction of PBO were reported in 5.5% of patients in the PBO + ENZ group (Table 4).

Table 4 Summary of dose modifications of TAL or placebo due to AEs in TALAPRO-2 (Cohort 2 – ITT HRR deficient)

Dose modifications, n (%)	TAL + ENZ N = 198	PBO + ENZ N = 199
Dose interruption due to AEs	114 (57.6%)	31 (15.6%)
Dose reduction due to AEs	103 (52.0%)	12 (6.0%)
Discontinuation due to AEs	20 (10.1%)	14 (7.0%)

Source: TALAPRO-2 CSR Cohort 2 Section 5.2.1.8 Dose Modifications
Abbreviations: AE, adverse event; CI, confidence interval; ENZ, enzalutamide; PBO, placebo; TAL, talazoparib

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator? (please select your response)

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

As discussed above, the current MBS items 73303 and 73304 for BRCA mutation testing are not expected to be substituted. BRCA mutation testing in mCRPC to determine eligibility for PBS-listed olaparib is expected to continue to be performed in the future, and the listing of talazoparib on the PBS will not alter the utilisation of this service. However, it is anticipated that the listing of talazoparib on the PBS will incur additional costs to the PBS because it is an add-on therapy to an existing therapy (enzalutamide) on the PBS and the use of this combination in mCRPC patients with BRCA1/2 gene mutation results in an increase in treatment duration.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

Do not attach full text articles; just provide a summary (repeat columns as required).

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
Pivotal study					
1	Randomised Phase III trial	Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial ClinicalTrials.gov NCT03395197	The purpose of this study is to evaluate the efficacy and safety (including evaluating side effects) of combination of talazoparib and enzalutamide versus placebo and enzalutamide in patients with metastatic castration resistant prostate cancer (mCRPC)	https://pubmed.ncbi.nlm.nih.gov/37285865/	Agarwal et al 2023 Lancet. 2023 Jul 22;402(10398):291-303
Diagnostic studies					
2	Diagnostic study	Early On-treatment Changes in Circulating Tumor DNA Fraction and Response to Enzalutamide or Abiraterone in Metastatic Castration-Resistant Prostate Cancer.	Plasma cell-free DNA was collected from 81 patients with mCRPC at baseline and after 4 weeks of first-line ARPI treatment during two prospective multicenter observational studies (NCT02426333; NCT02471469). ctDNA fraction was calculated from somatic mutations in targeted sequencing and genome copy-number profiles. ctDNA was detected in 48/81 (59%) baseline and 29/81 (36%) 4-week samples. ctDNA fraction for samples with detected ctDNA was lower at 4 weeks versus baseline (median 5.0% versus 14.5%, P = 0.017). PFS and OS were shortest for patients with persistent ctDNA at 4 weeks (univariate HR, 4.79; 95% CI, 2.62-8.77 and univariate HR, 5.49; 95% CI, 2.76-10.91, respectively), independent of clinical prognostic factors	https://pubmed.ncbi.nlm.nih.gov/36996325/	Tolmeije et al, 2023 Clin Cancer Res. 2023 Aug 1;29(15):2835-2844

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3	Diagnostic study	Germline DNA Repair Gene Mutation Landscape in Chinese Prostate Cancer Patients	Landscape of 18 germline DNA repair gene mutation in 316 Chinese patients with prostate cancer. Among all cases, 9.8% (31/316, 95% confidence interval [CI]: 6.5–13%) carried pathogenic mutations in 18 PCa-related DRGs: 6.3% in BRCA2, 0.63% in BRCA1, 0.63% in ATM, and 2.5% in 15 other genes. Overall, study observed similar germline DRG mutation frequencies, although there is large disparity in the risk of PCa between China and the West.	https://www.sciencedirect.com/science/article/pii/S0302283819304531	Wei,Y. et al, 2019 European Urology Volume 76, Issue 3, September 2019, Pages 280-28
4	Diagnostic study	Germline DNA-repair Gene Mutations and Outcomes in Men with Metastatic Castration-resistant Prostate Cancer Receiving First-line Abiraterone and Enzalutamide	To determine whether and how germline DNA-repair gene mutations influence clinical outcomes to abiraterone or enzalutamide in patients with castration-resistant prostate cancer using germline genotyping for 50 DNA repair genes using blood samples from 172 patients with CRPC beginning first-line systemic therapy with abiraterone or enzalutamide.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6045965/	Antonarakis et al, 2018 Eur Urol. 2018 Aug; 74(2): 218–225.
5	Diagnostic study	Treatment Outcomes and Tumor Loss of Heterozygosity in Germline DNA Repair-deficient Prostate Cancer	To determine the clinical response of 319 mCRPC patients with germline DNA repair defects to androgen receptordirected therapies and to establish whether biallelic DNA repair gene loss is detectable in matched circulating tumour DNA.	https://www.ncbi.nlm.nih.gov/pubmed/28259476	Annala et al, 2017 Eur Urol. 2017 Jul;72(1):34-42
6	Diagnostic study	Inherited DNA-repair gene mutations in men with metastatic prostate cancer	Multicentre study that recruited 692 men with metastatic prostate cancer who were unselected for family history of cancer or age at diagnosis. Germline DNA was isolated and used multiplex sequencing assays to assess mutations in 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes.	https://www.nejm.org/doi/full/10.1056/NEJMoa1603144	Pritchard et al, 2016 N Engl J Med 2016; 375:443-453

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
7	Diagnostic study	Circulating tumor DNA (ctDNA) burden and actionable mutations in treatment-naive metastatic castration-resistant prostate cancer (mCRPC)	Collection of baseline cellfree DNA (cfDNA samples from 36 chemotherapy-naive mCRPC patients enrolled in an ongoing randomised phase II crossover trial of abiraterone vs enzalutamide (NCT02125357) and performed deep targeted sequencing using a custom NimbleGen SeqCap EZ Choice panel of 72 mCRPC-related genes	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01267739/full	Wyatt et al, 2016 Journal of clinical oncology 2016; Volume:34
8	Diagnostic study	Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer	Randomisation of 202 patients with treatment-naïve mCRPC to abiraterone or enzalutamide for whole exome and deep targeted 72 gene sequencing of plasma cell free DNA prior to therapy.	https://pubmed.ncbi.nlm.nih.gov/29367197/	Annala et al, 2017 Cancer Discov. 2018 Apr;8(4):444-457.
9	Diagnostic study	Abiraterone + prednisone (Abi) +/- veliparib (Vel) for patients (pts) with metastatic castration-resistant prostate cancer (CRPC): NCI 9012 updated clinical and genomics data	148 patients had metastatic disease biopsy, stratified by IHC-ETS status and randomised to Abi (Arm A) or Abi + Vel (Arm B). Primary endpoint: PSA response rate (RR > = 50% decline). Secondary endpoints: safety, objective RR (ORR), progression free survival (PFS), and molecular analysis including if DNA repair gene deficiency (DRD: BRCA 1, BRCA 2, ATM, FANCA, PALB2, RAD51B, RAD51C) predicts response.	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01750310/full	Hussain et al, 2017. Journal of clinical oncology, 2017 Volume:35
10	Diagnostic study	Genomic alterations in circulating tumor DNA (ctDNA) are associated with clinical outcomes in treatment naive metastatic castration-resistant prostate cancer (mCRPC) patients commencing androgen receptor (AR)-targeted therapy	Deep targeted sequencing of 72 mCRPC-related genes in baseline cfDNA from 62 chemotherapy-naïve mCRPC patients enrolled in an ongoing randomised phase II trial of abiraterone vs enzalutamide (NCT02125357). Genomic alterations in cfDNA were examined for association with clinical variables including time on treatment.	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01295966/full	Wyatt et al, 2016 Annals of oncology, 2016, Volume 27.
11	Diagnostic study	Co-targeting androgen receptor (AR) and DNA repair: a randomized ETS gene fusion-stratified trial of	148 eligible mCRPC patients underwent metastatic disease biopsy, were stratified by ETS status and randomised to Abi (Arm A) or Abi +	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01733597/full	Hussain et al, 2016

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
		abiraterone + prednisone (Abi) +/- the PARP1 inhibitor veliparib for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) (NCI9012)-A University of Chicago phase II consortium trial	Veliparib (Arm B). The primary endpoint was confirmed PSA response rate. Secondary endpoints included safety, objective RR (ORR), progression free survival (PFS), and if DNA repair gene deficiency (DRD; homozygous deletions or deleterious mutations: BRCA 1, BRCA 2, ATM, FANCA, PALB2, RAD51B, RAD51C) predicts response.		Journal of clinical oncology, 2016, 34.
Other studies					
12	Phase II trial	BRCAAWAY: A randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) with DNA repair defects. Clinical trial information: NCT03012321	61 pts had NGS testing; 60 pts were randomized to Arms 1-3; to date 59 are evaluable for toxicity and 53 are evaluable for PFS. Mutational status: BRCA1 only n = 2, BRCA2 only n = 39, ATM only n = 8, and > 1 HRRm n = 11. 34 pts had germline and 26 had somatic mutations. In mCRPC pts with inactivating BRCA1, BRCA2 and/or ATM alterations Abi/pred + olaparib was well tolerated and resulted in longer PFS and better PSA response vs either agent alone.	https://ascopubs.org/doi/10.1200/JCO.2022.40.16_suppl.5018	Hussain et al, 2022 ASCO 2022 Conference abstract
13	Prospective report	Circulating cell-free DNA to guide prostate cancer treatment with PARP inhibition	Areport on prospectively planned, serial, cfDNA analyses from patients with metastatic prostate cancer treated on an investigator-initiated phase II trial of olaparib. These analyses provide predictive, prognostic, response, and resistance data with "second hit" mutations first detectable at disease progression.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6143169/	Goodall et al, 2017 Cancer Discov. 2017 Sep; 7(9): 1006–1017.
14	Case series	Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of BRCA2 Reversion Mutations Associated with Resistance to PARP Inhibitors	Identification of BRCA2 reversion mutations associated with olaparib and talazoparib resistance in prostate cancer patients.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5581695/	Quigley et al, 2017 Cancer Discov. 2017 Sep; 7(9): 999–1005.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
Reviews					
15	Review	Targeting the DNA damage response: PARP inhibitors and new perspectives in the landscape of cancer treatment	Summary of the main DDR pathways, explain the current role of PARP inhibitors in cancer therapy and illustrate new therapeutic strategies targeting the DDR, focusing on the combinations of PARP inhibitors with other agents and on cell-cycle checkpoint inhibitors.	https://pubmed.ncbi.nlm.nih.gov/34800653/	Genta et al 2021 Crit Rev Oncol Hematol. 2021 Dec;168:103539
16	Review	Recent advances in DNA repair pathway and its application in personalized care of metastatic castration-resistant prostate cancer (mCRPC).	Review focused on recent advances in biology and clinical implication of DDR pathway and discuss the latest results in advanced prostate cancer, especially mCRPC	https://pubmed.ncbi.nlm.nih.gov/32710316/	Xu et al. 2020 Methods Mol Biol. 2020; 2204:75-89
17	Review	PARP inhibitors in prostate cancer: The preclinical rationale and current clinical development	Overview of published and ongoing trials exploring PARP inhibitors in treatment of prostate cancer and discuss the underlying biology	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6723995/	Virtanen. *et al.* 2019 Genes (Basel). 2019 Aug; 10(8): 565
18	Review	Recent advances in prostate cancer research: Large-scale genomic analyses reveal novel driver mutations and DNA repair defects	Review of the recent advances in prostate cancer research, including understanding the genetic alterations that drive the disease and how specific mutations can sensitise tumours to potential therapies.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6073096/	Sander et al, 2018 F1000Research 2018, 7(F1000 Faculty Rev):1173
19	Review	A decade of clinical development of PARP inhibitors in perspective	Summary of a decade of PARP inhibitor clinical development.	https://www.sciencedirect.com/science/article/pii/S0923753419459851?via%3Dihub	Mateo et al, 2019 Ann Oncol. 2019 Sep 1;30(9):1437-1447
20	Review	DNA repair defects in prostate cancer: impact for screening, prognostication and treatment	Review covers the relationship between DNA repair defects and prostate cancer, highlighting the prevalence of mutations in key genes and their controversial association with clinical outcomes.	https://www.ncbi.nlm.nih.gov/pubmed/30281887/	Warner et al, 2019 BJU Int. 2019 May;123(5):769-776

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
21	Review	Targeting DNA Repair Defects for Precision Medicine in Prostate Cancer	Review of the current knowledge on DNA repair defects in prostate cancer and an overview of how these alterations can be targeted towards a personalised prostate cancer management	https://pubmed.ncbi.nlm.nih.gov/30919167/	Athie et al. 2019 Curr Oncol Rep. 2019 Mar 27;21(5):42
22	Review	DNA damage repair: An emerging strategy in metastatic prostate cancer	Review in prostate cancer discussing DNA repair abnormalities which mainly correspond to somatic or constitutional mutations of the BRCA2 and ATM genes. Therapeutic management of metastatic castration resistant prostate cancer (mCRPC) is currently based on new hormonal therapies and taxane-type chemotherapy	https://pubmed.ncbi.nlm.nih.gov/30278883/	Loriot et al, 2018 Bull Cancer. 2018 Oct;105(10):944-954

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Randomised Phase III trial	Talapro-3: A phase 3, double-blind, randomized study of enzalutamide (ENZA) plus talazoparib (TALA) versus placebo plus enza in patients with DDR gene mutated metastatic castration-sensitive prostate cancer (mCSPC). ClinicalTrials.gov NCT04821622	The purpose of this study is to evaluate the efficacy and safety (including evaluating side effects) of combination of talazoparib and enzalutamide versus placebo and enzalutamide in patients with metastatic castration resistant prostate cancer (mCRPC) with DDR gene mutations	Study of Talazoparib With Enzalutamide in Men With DDR Gene Mutated mCSPC - Full Text View - ClinicalTrials.gov	2026

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