MSAC Application 1788

ArteraAI Prostate Biopsy Assay for patients with localised prostate cancer

Applicant: Artera Inc.

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an assessment report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for ArteraAI Prostate Biopsy Assay in patients with localised prostate cancer of intermediate risk

Component	Description
Population	Patients with histologically confirmed localised prostate cancer, classified as having intermediate-risk disease, who are planned for curative-intent RT, and who have not yet received treatment with curative intent. Intermediate-risk disease includes patients with at least one of the following intermediate risk factors:[1] • Clinical stage cT2b or cT2c • Grade Group 2 or 3 (Gleason Score 7 [3+4] or Gleason Score 7 [4+3]) • PSA 10 to 20 ng/mL.
Prior tests	Conventional diagnostic approaches for the diagnosis, staging, grading and risk stratification of prostate cancer. Prior tests include PSA testing, digital rectal exam, prostate MRI and prostate core needle biopsy. Additional imaging scans as required for staging. Cancer stage, Gleason score and baseline PSA are required inputs into the algorithms. H&E-stained slides of core needle biopsy FFPE specimens are required. Biopsy specimens used by proposed investigative intervention must be treatment-naïve.
Intervention	ArteraAI Prostate Biopsy Assay (prognostic and predictive models) Inputs for the ArteraAI algorithms comprise clinical variables as well as data from digital WSIs. Clinical variables comprise age, PSA, tumour stage ± Gleason score.[2]
Comparator/s	Predictive model: current standard of care treatment decision-making processes for deciding whether to use ST-ADT in addition to RT (guided by NCCN or EAU guidelines). Prognostic model: for assessment of prognostic accuracy of the prognostic algorithms, standard of care risk classification systems, including the NCCN or EAU risk groups, are relevant comparators.
Reference standard	Predictive model: whether test-result positive and negative patients respond differently to the addition of ST-ADT as an adjunct therapy vs RT alone. Prognostic model: rate of development of distant metastasis (at 10 years) or the rate of PCSM (at 10 years).

[1] Intermediate risk disease as defined by National Comprehensive Cancer Network (NCCN) guidelines. The European Association of Urology (EAU) guideline definition is largely the same, except for clinical stage T2c, which is considered a high-risk feature by the EAU. Both guidelines are accepted clinically.

[2] The algorithms of the ArteraAI Prostate Biopsy Assay have had version updates. Gleason scores were included as clinical variables in earlier versions of the prognostic and predictive models; however, were later removed from the prognostic model (Gerrard et al. 2024).

Component	Description
Outcomes	*Effectiveness outcomes* *Test accuracy of the predictive model* • Test reliability: inter- and intra-operator reliability; inter- and intra-scanner reliability (e.g. per cent agreement) • Predictive accuracy (with reference to treatment response in test-result positive and negative patients) *Test accuracy of the prognostic model* • Test reliability: inter- and intra-operator reliability; inter- and intra-scanner reliability (e.g. using ICC) • Longitudinal accuracy with reference to health outcome of interest (distant metastasis, PCSM) at a later timepoint (e.g. using area under the curve for time-dependent receiver operator characteristics of sensitivity and specificity) *Comparative effectiveness in selecting patients for RT + ST-ADT treatment* *Change in clinical management* • Change in the proportion of patients referred for or treated with RT + ST-ADT or RT alone *Patient-centred health outcomes* • Change in overall survival • Change in prostate cancer-specific survival • Change in occurrence of distant metastases • Change in biochemical failure/recurrence (increasing PSA) defined by the Phoenix definition of nadir +2 ng/mL (blood PSA measurement) • Change in patient-reported health status (e.g. EPIC-26)/QoL *Safety outcomes* • AEs of treatment with ST-ADT • Harms (psychological health risks) associated with testing *Value of knowing* • Knowledge of prognosis for future planning/patient decisions *Healthcare system outcomes* • Costs associated with the ArteraAI Prostate Biopsy Assay (in addition to standard care) • Costs of treatments received/cost offsets from avoidance of ST-ADT • Costs associated with management of ST-ADT-related AEs • Cost-effectiveness
Assessment question	What is the safety, effectiveness and cost-effectiveness of the ArteraAI Prostate Biopsy Assay as an add-on to current clinical practice vs current clinical practice alone for predicting prognosis and for informing which patients with localised prostate cancer of intermediate risk planning to receive curative intent RT are treated with ST-ADT? Including assessments of the following:

Component	Description
	• What is the accuracy of the ArteraAI Prostate Biopsy Assay in predicting which patients with localised prostate cancer of intermediate risk planning to receive curative-intent RT are likely to benefit from the addition of ST-ADT, compared to current clinical practice? • What is the accuracy of the ArteraAI Prostate Biopsy Assay in predicting long-term outcomes (distant metastases and PCSM) in patients with localised prostate cancer of intermediate risk planning to receive curative-intent RT, compared to current risk classification systems (e.g. NCCN or EAU risk groups)? • How does the use of the ArteraAI Prostate Biopsy Assay affect clinical decision-making and impact health outcomes (e.g. survival, QoL, disease progression) in patients with localised prostate cancer of intermediate risk planning to receive curative-intent RT, compared to current clinical practice?

AE = adverse event, EAU = European Association of Urology, EPIC-26 = Expanded Prostate Cancer Index Composite (26-item version), FFPE = formalin-fixed, paraffin-embedded, H&E = haematoxylin and eosin, ICC = intraclass correlation coefficient, MRI = magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, PCSM = prostate cancer-specific mortality, PSA = prostate-specific antigen, QoL = quality of life, RT = radiotherapy; ST-ADT = short-term androgen deprivation therapy, WSI = whole slide image.

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of the ArteraAI Prostate Biopsy Assay was received from Artera Inc. by the Department of Health and Aged Care.

The intent of the test for the purposes of this application is to inform prognosis and treatment decisions regarding use of short-term androgen deprivation therapy (ST-ADT) in the patient population of interest, that is, patients with histologically confirmed localised prostate cancer of intermediate risk who are planned for curative-intent radiotherapy (RT).

The ArteraAI Prostate Biopsy Assay is a software device based on artificial intelligence (AI) that assesses clinician-provided clinical variables and whole slide images (WSI) of prostate core needle biopsy specimens. The test then provides the following outputs:

- Prognostic model: classification of patients into risk groups (low, intermediate, high) based on risk estimates of distant metastasis and prostate-cancer-specific mortality for patients with prostate cancer.
- Predictive model: prediction of whether a patient with intermediate risk (according to the National Comprehensive Cancer Network [NCCN] classification) is more likely to benefit from the addition of ST-ADT.

The following claims were made by the applicant (personal communication, applicant, 23 November 2024):

- Compared to standard care, the ArteraAI Prostate Biopsy Assay prognostic model has superior discriminatory performance for distant metastasis and prostate cancer-specific survival, thereby improving the value of knowing for patients.
- The ArteraAI Prostate Biopsy Assay predictive model is superior to standard care in predicting response to ST-ADT as an additional treatment to curative RT.
- The test results will lead to superior health outcomes because the combined use of both models will ensure patients unlikely to benefit from additional ST-ADT treatment can avoid the negative consequences of treatment and those likely to benefit will receive treatment with ST-ADT.

Therapeutic Goods Administration (TGA) approval is being sought via an application (ID: DV-2024-IVA-07137-1) submitted 15 March 2024. The population included in the TGA application is broader than the population included in this application. The indication for the ArteraAI Prostate Biopsy Assay as per the instructions for use is as follows (personal communication, applicant, 23 November 2024):

> 'The ArteraAI Prostate Biopsy Assay is intended for adult males 18 years of age or older with localised prostate cancer, without clinically or pathologically defined metastases. The intended patient should also be a candidate for curative intent management (surgery, radiation therapy ± systemic therapy, or active surveillance). The ArteraAI Prostate Biopsy Assay is intended to assist clinicians with risk-based decisions in localised prostate cancer within recommended clinical guidelines.'

PICO criteria

Population

The patient population comprises those with histologically confirmed localised prostate cancer classified as having intermediate-risk disease (based on the European Association of Urology [EAU] or NCCN risk

groupings) who are planned for curative-intent radiotherapy and have not yet received treatment with curative intent. This includes patients with at least one of the following intermediate-risk factors (IRFs), as defined by 2024 NCCN guidelines (NCCN 2024a):[3]

- clinical stage cT2b or cT2c
- Grade Group 2 or 3 (Gleason Score 7 [3+4] or Gleason Score 7 [4+3])
- prostate-specific antigen (PSA) 10 to 20 ng/mL.

Intermediate-risk patients can be further categorised into 2 groups based on NCCN risk grouping:

- **Favourable intermediate-risk**: patients with 1 IRF, Grade Group 1 or 2 (Gleason Score ≤6 or Gleason Score 7 [3+4]), and <50% biopsy cores positive (e.g. <6 of 12 cores).
- **Unfavourable intermediate-risk**: patients with 2 or 3 IRFs, Grade Group 3 (Gleason Score 7 [4+3]), or ≥50% biopsy cores positive.

Favourable intermediate-risk patients are candidates for more conservative and localised treatment, involving active surveillance or radiotherapy alone (NCCN 2024a). Conversely, unfavourable intermediate-risk patients may benefit from more intensified therapy, such as combined radiotherapy and ST-ADT (i.e. 4–6 months of androgen deprivation therapy [ADT]), to address their increased likelihood of progression or recurrence (details in Management of localised prostate cancer of intermediate risk section).

The ArteraAI Prostate Biopsy Assay is designed for patients diagnosed with any localised prostate cancer (ARTERA 2024). The claim is that it can inform prognosis and provide risk classification. Additionally, for patients with intermediate-risk disease, it makes a prediction about those patients more or less likely to benefit from ST-ADT in combination with RT. The population targeted by the current application is restricted to patients that may benefit from both the prognostic and predictive components of the ArteraAI assay (i.e. patients with intermediate-risk planning to receive curative-intent RT, see Rationale of the proposed population).

The ArteraAI Prostate Biopsy Assay is unsuitable for patients with a diagnosis of advanced-stage (regional and metastatic) prostate cancer or those who have undergone previous curative-intent treatment (ARTERA 2024).

Context

Use of the ArteraAI Prostate Biopsy Assay in the proposed population is intended to enhance clinical decision-making for intermediate-risk localised prostate cancer patients by providing an additional tool to better assess the benefit and risk of adding ST-ADT to planned curative RT (Nguyen et al. 2015). Evidence from studies, including findings by Gerrard et al. (2024), suggests that many intermediate-risk patients may not derive significant clinical benefit from the addition of hormone therapy. The proposed assay aims to stratify those patients who are most likely to benefit from the additional treatment, aiding clinicians in managing potential side effects associated with ST-ADT such as sexual dysfunction, osteoporosis and cardiovascular risk (ARTERA 2024; Nguyen et al. 2015).

The proposed population aligns with the current diagnostic and treatment workflow for localised prostate cancer, as patients typically undergo evaluation by a urologist followed by a needle biopsy,

[3] The EAU guideline definition for intermediate risk is largely the same, except for clinical stage T2c, which is considered a high-risk feature by the EAU. The EAU guideline does not stratify intermediate risk into favourable and unfavourable groups.

histopathological analysis and Gleason score assignment. To integrate the assay, pre-treatment biopsy specimens must be digitised to WSIs before being analysable by the AI software, which may introduce an additional step to the workflow. If biopsy specimens have already been digitised to WSIs for clinical risk assessments, these same WSIs from prostate needle biopsy samples can be utilised for the assay. If not, the tissue slides obtained from biopsy specimens would be scanned to create WSIs. Currently, only 2 scanners have been validated for use by the applicant, so slides may need to be referred to central laboratories that have one of these scanners, with likely additional costs.

Background

Prostate cancer is the uncontrolled growth of abnormal cells in the prostate gland, commonly occurring in older men (Cancer Council 2024). Potential symptoms include blood in the urine or semen, pain or burning during urination, unexplained weight loss, and pain in the bones, hips or back (NCCN 2024a). Localised prostate cancer is often asymptomatic and slow-growing, but intermediate-risk patients may face a more uncertain prognosis, making effective treatment decisions critical.

Staging (macro level)

The most common staging system for prostate cancer is the tumour node metastasis (TNM) system, which describes a tumour's size and spread, with larger numbers indicating greater size or spread (Table 2). Localised prostate cancer often grows slowly and stays confined within the prostate gland (T1 or T2, Table 3). In some cases, however, prostate cancer can grow more rapidly, spreading beyond the prostate to nearby areas such as the bladder or rectum, nearby lymph nodes, or more distant parts of the body such as bones, liver or lung (Cornford et al. 2024; NCCN 2024a).

Table 2: Clinical TNM classification of prostate cancer

Category		Description
T – Primary Tumour (stage based on DRE only)		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1		Clinically inapparent tumour that is not palpable
	T1a	Tumour incidental histological finding in ≤5% of tissue resected
	T1b	Tumour incidental histological finding in >5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. elevated PSA)
T2		Tumour that is palpable and confined within the prostate
	T2a	Tumour involves half of one lobe or less
	T2b	Tumour involves more than half of one lobe but not both lobes
	T2c	Tumour involves both lobes
T3		Tumour extends palpably throughout the prostatic capsule
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4		Tumour is fixed or invades adjacent structures other than seminal vesicles (e.g. external sphincter, rectum, levator muscle and/or pelvic wall)
N – Regional (pelvic) Lymph Nodes		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
M – Distant Metastasis		
M0		No distant metastasis
M1		Distant metastasis
	M1a	Non-regional lymph nodes
	M1b	Bone(s)
	M1c	Other site(s)

DRE = digital rectal examination, PSA = prostate-specific antigen, TNM = tumour node metastasis
Source: Application form, p.2 of the PICO Set, based on EAU guidelines on prostate cancer (Cornford et al. 2024).

Table 3: Prostate cancer type (early-stage and advanced) vs corresponding TNM classification

Category	TNM stage	Description
Localised (early stage)	T1 or T2, N0, M0	Cancer contained inside prostate
Regional (locally advanced)	N1, M0	Cancer is larger and has spread outside prostate to nearby lymph nodes
Metastatic	N1 or N2, M1	Cancer has spread to distant parts of the body such as bladder, rectum, pelvic wall or bone

TNM = tumour node metastasis
Note: Regional prostate cancer is used in this PICO to avoid confusion between localised and locally advanced.
Source: NCCN clinical practice guidelines (NCCN 2024a) and the PCOR–ANZ Annual Report 2023 (Ong et al. 2024).

Grading (micro level)

Prostate cancer is graded using the Gleason score and the International Society of Urological Pathology (ISUP) Grade Group system, both of which assess how aggressive a cancer is based on the microscopic

appearance of the cancer cells. Higher scores indicate a more aggressive cancer (Cancer Council 2024; Srigley et al. 2016).

Gleason Score

The Gleason score is determined based on a biopsy performed by a physician (urologist). A pathologist examines the biopsy specimen and assigns a primary Gleason grade to the most predominant cancer pattern, as well as a secondary Gleason grade to the next most common pattern. These two grades are then summed to form the Gleason score (e.g. 3 + 4). In theory, Gleason scores can range from 2 to 10 but, in practice, pathologists rarely assign scores of 2 to 5. As a result, Gleason scores typically range from 6 to 10, with 6 being the lowest grade for cancer (2024 Canadian Cancer Society 2021; NCCN 2024a).

ISUP Grade Group System

The ISUP Grade Group system is a simplified grading system for prostate cancer, based on the grouping of Gleason scores and Gleason patterns (Table 4). Introduced in 2014 by ISUP, it was designed to replace the traditional Gleason scoring system. While many hospitals now report both the Gleason score and the Grade Group, the Gleason score remains prevalent in practical use worldwide (Offermann et al. 2020). In Australia, expert advice from a local clinician indicated that the ISUP Grade Group system is the preferred method for grading prostate cancer (personal communication, expert urologist, 30 October 2024).

Table 4: ISUP Grade Group system

ISUP Grade	Gleason score	Description
Grade 1	2–6	Only individual discrete well-formed glands
Grade 2	3+4=7	Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
Grade 3	4+3=7	Predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands
Grade 4	4+4=8	Only poorly formed/fused/cribriform glands
	3+5=8	Predominantly well-formed glands and lesser component lacking glands (or with necrosis)
	5+3=8	Predominantly lacking glands (or with necrosis) and lesser component of well-formed glands
Grade 5	9–10	Lacking gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

ISUP = International Society of Urological Pathology
Source: (Cancer Council 2024); (Srigley et al. 2016)

Risk Stratification

By combining staging and grading with factors such as PSA levels, prostate cancer risk stratification helps with disease management and guides treatment options (Cornford et al. 2024). Management options range from active surveillance for low-risk cases to more aggressive treatments such as surgery, radiation or systemic therapies for high-risk or metastatic cancer. In Australia, risk stratification is established by urologists or radiation oncologists who are making treatment decisions based on the current standard of care (Application form, p.10 of the PICO Set).

A variety of risk classification systems are available, including those from the NCCN (NCCN 2024a), the American Urological Association (AUA) (Eastham et al. 2022) and the EAU (Cornford et al. 2024). In Australia, the Urological Society of Australia and New Zealand (USANZ) has endorsed the EAU guidelines for prostate cancer (Urological Society of Australia and New Zealand 2024), while oncologists in Australia manage prostate cancer following the NCCN guidelines for risk assessment and management (Application form, p.10 of the PICO Set).

Both the EAU and NCCN risk group classifications are based on D'Amico's classification system, which was created after a review of the literature and initially validated for biochemical recurrence (Cornford et al. 2024; NCCN 2024b). According to EAU and NCCN guidelines, the most common risk groupings are low-risk, intermediate-risk, high-risk and very high-risk (or metastatic). Although both guidelines are largely similar (Table 5), a key difference is that the NCCN guidelines stratify intermediate-risk patients into categories of favourable/unfavourable, while the EAU guidelines do not (Application form, p.10 of the PICO Set). The EAU guidelines refer to the NCCN guidelines with respect to treatment recommendations for those with favourable/unfavourable intermediate risk (see Management of localised prostate cancer of intermediate risk).

Table 5: NCCN and EAU risk groupings

Risk group	NCCN description	EAU description
Low risk	T1–T2a, GS ≤6 and PSA <10 ng/mL	T1–2a* GS <7 (ISUP grade 1) and PSA <10 ng/mL
Intermediate risk	T2b–T2c or GS 7 or PSA 10–20 ng/mL	T2b* GS 7 (ISUP grade 2/3) or PSA 10–20 ng/mL
Favourable intermediate risk	All of the following: 1 IRF, Grade Group 1 or 2 (GS <6 or GS 7), <50% biopsy cores positive (e.g. <6 of 12 cores)	N/A^
Unfavourable intermediate risk	At least one of the following: 2 or 3 IRFs, Grade Group 3 (GS 7), >50% biopsy cores positive (e.g. ≥6 of 12 cores)	N/A^
High risk	T3a or GS 8–10 or PSA >20 ng/mL	T2c, T3–4 or GS >7 (ISUP grade 4/5) or N+** PSA >20 ng/mL or any PSA, any GS (any ISUP grade)
Very high risk	T3b–T4 or primary Gleason pattern 5 or >5 cores with GS 8–10 and metastatic risk N1 or M1 with any T stage	N/A

EAU = European Association of Urology, GS = Gleason score, IRF = intermediate risk factor, ISUP = International Society of Urological Pathology, PSA = prostate-specific antigen, NCCN = National Comprehensive Cancer Network
Notes: *Based on digital rectal examination
**Based on CT/bone scan
^EAU guidelines do not separate intermediate risk into favourable and unfavourable; however, some EAU treatment recommendations are separated by NCCN into favourable/unfavourable risk categories.
Source: Application form, p.4 of the PICO Set, based on information in NCCN and EAU clinical practice guidelines (Cornford et al. 2024; NCCN 2024a).

The PICO Advisory Subcommittee (PASC) noted challenges in defining the percentage of positive biopsy cores (one criterion used to distinguish favourable and unfavourable intermediate risk) given cores are fragile and frequently fragmented. PASC noted a need for clearer Royal College of Pathologists of Australasia (RCPA) scoring guidelines around this and suggested it may be important whether the core biopsies are magnetic resonance imaging (MRI) targeted or not.

Disease burden

Prostate cancer is the most commonly diagnosed cancer among Australian men. The Australian Institute of Health and Welfare (AIHW) estimates that 26,400 men will be diagnosed with the disease in 2024, accounting for 28% of the cancers to be diagnosed in males for the year. The age-standardised incidence

rate is projected to be 204.4 per 100,000 men (97.1 per 100,000 people) (Australian Institute of Health and Welfare 2024). Of newly diagnosed cases, approximately 87–94% are localised prostate cancer (stage T1 or T2), according to national and state data from Australia (Evans et al. 2013; National Cancer Control Indicators 2021; Smith et al. 2009; Weerakoon et al. 2015).

Prostate cancer is also the second leading cause of cancer-related deaths among Australian men, behind lung cancer (Prostate Cancer Foundation of Australia 2024). The AIHW reported that in 2024, prostate cancer was expected to cause approximately 3,900 deaths (National Mortality Database) (Australian Institute of Health and Welfare 2024), equating to an age-standardised mortality rate of 33.1 per 100,000 men (14.4 per 100,000 people). Although the number of deaths continues to rise, mortality rates have been decreasing over past decades. For comparison, in 2000 there were around 2,700 deaths from prostate cancer, equating to an age-standardised mortality rate of 51.6 per 100,000 men (19.9 per 100,000 people) (Australian Institute of Health and Welfare 2024).

The overall 5-year relative survival rate for men diagnosed with prostate cancer between 2016 and 2020 was 95.8% (95% CI: 95.5–96.0%), meaning that 95.8% of men with prostate cancer survived 5 years post-diagnosis, compared to the general population (Australian Institute of Health and Welfare 2024). The high survival rate was largely driven by the 5-year survival rate for adenocarcinomas (98%), which comprised over 96% of prostate cancer cases in 2020. The 5-year survival rate for neuroendocrine neoplasms between 2016 and 2020 was 9.9%; these cancers accounted for 0.1% of all prostate cancer cases (Australian Institute of Health and Welfare 2024). For those diagnosed with T1–3 disease, the 5-year survival rate was nearly 100%; for men with T4 disease, it dropped significantly to 36% (National Cancer Control Indicators 2019).

Management of localised prostate cancer of intermediate risk

Based on NCCN guidelines, the current standard of care for men with intermediate-risk prostate cancer includes observation, active surveillance, prostate surgery and RT alone or in combination with adjuvant ADT (NCCN 2024a). For men with intermediate-risk disease and the intention to undergo curative-intent RT, the decision to use ST-ADT is made by weighing the benefits against the risks, taking life expectancy into account (Table 6). The use of RT alone should be considered in patients with lower-risk cancers, whereas those with higher-risk cancers should consider the addition of ST-ADT (NCCN 2024a).

Table 6: Initial therapy options for intermediate-risk prostate cancer, based on NCCN guidelines

Group	≥10 years expected patient survival	5–10 years expected patient survival
Favourable intermediate-risk group (lower risk)	• Active surveillance (preferred) • Radical prostatectomy ± pelvic lymph node dissection (assessed using nomogram)* • RT (either EBRT or brachytherapy)	• Observation (preferred) • RT (either EBRT or brachytherapy)
Unfavourable intermediate-risk group (higher risk)	• Radical prostatectomy ± pelvic lymph node dissection (assessed using nomogram)* • RT (either EBRT or brachytherapy) + ST-ADT	• Observation • RT (either EBRT or brachytherapy) + ST-ADT

EBRT = external-beam radiotherapy, NCCN = National Comprehensive Cancer Network, RT = radiotherapy, ST-ADT = short-term androgen deprivation therapy

Notes: *Patient may require additional treatment or adjuvant therapy, which may include EBRT ± ADT, when high-risk features are identified after prostate surgery. This additional treatment helps reduce the risk of cancer recurrence. High-risk features include a) cancer in the normal-looking tissue removed with the tumour (surgical margin), b) cancer outside the layer surrounding the prostate, c) cancer in the seminal vesicle(s), d) cancer in the lymph nodes (i.e. lymph node metastasis) or e) a detectable level of PSA.

Source: NCCN clinical practice guidelines (NCCN 2024a)

According to EAU guidelines, management of intermediate-risk prostate cancer is based on life expectancy and disease characteristics (Cornford et al. 2024). Watchful waiting is recommended for asymptomatic patients with a life expectancy of <10 years, based on comorbidities and age. For those with a life expectancy >10 years, radical prostatectomy is a highly recommended option. Patients with good urinary function and NCCN favourable intermediate-risk disease can be offered low dose rate (LDR) brachytherapy, while those with NCCN unfavourable intermediate-risk disease may benefit from LDR or high dose rate (HDR) brachytherapy combined with intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) and image-guided RT (IGRT), along with ST-ADT. ADT monotherapy should not be offered to asymptomatic men who are unable to undergo any local treatment (i.e. radical prostatectomy or RT) (Cornford et al. 2024).

PASC noted that the proposed population included patients with both favourable and unfavourable intermediate-risk localised prostate cancer, as classified by the NCCN guidelines. PASC considered if the proposed population should be limited to patients with unfavourable intermediate-risk disease. PASC noted input from the applicant's clinical experts that there is currently considerable overlap between the favourable and unfavourable intermediate-risk groups in terms of distant metastasis risk, which has been observed in the ASTuTE (Artificial intelligence Steering Testosterone deprivation Treatments in prostate cancer External-beam radiotherapy) trial. The applicant's clinical expert explained that in clinical practice many patients fall on the cusp of favourable or unfavourable risk and that the NCCN guideline flowcharts currently do not capture these grey areas. Furthermore, the applicant's clinical expert detailed that these 'grey areas' are where the use of ArteraAI can provide additional information to guide the clinician's decision-making process—as observed in the ASTuTE trial. PASC noted the applicant's preference to support the inclusion of both favourable and unfavourable risk groups in the proposed MBS item descriptor.

In Australia, treatment of localised prostate cancer of intermediate risk falls outside the conditions specified in the Australian Register of Therapeutic Goods (ARTG) listings for ADT, and ADT is not currently listed on the Pharmaceutical Benefits Scheme (PBS) for patients with intermediate-risk prostate cancer. Nevertheless, a significant proportion of patients with intermediate-risk prostate cancer may still receive off-label ST-ADT in clinical practice (Application form, p.8 of the PICO Set). In 2021, according to the Prostate Cancer Across Australia and New Zealand annual report 2023, 16% of patients with intermediate-risk disease received RT and a further 9% received RT + ADT (Ong et al. 2024). (See Subsequent therapies in the Proposal for public funding section for further details).

PASC noted ADT is currently not PBS-listed for the proposed population. PASC noted input from a consumer representative expressing frustration around the systemic problem surrounding the absence of PBS listing of ADT in this population group, suggesting this could cause confusion for consumers.

PASC noted input from the applicant's clinical experts that use of ADT reflects current clinical practice; however, it was felt that currently there may be overuse of ADT in clinical practice (within this context). PASC noted preliminary results from the ASTuTE trial shared verbally at the PASC meeting, which show that of the patients recommended for ST-ADT before the assay, the shared ST-ADT decision was changed in 70% of patients after the ArteraAI Prostate Biopsy Assay. The applicant also shared an observation that validation data from North America is showing that most patients with intermediate-risk disease would be identified as unlikely to benefit from ST-ADT. PASC noted research from Krauss et al. (2023) suggesting most patients with intermediate-risk disease are unlikely to gain significant advantages from hormone therapy in terms of overall survival.

Estimated size of the eligible population

The application estimated that approximately 45% of newly diagnosed prostate cancer cases in 2023 were classified as NCCN intermediate-risk, according to data from the Prostate Cancer Outcomes Registry Australia and New Zealand (Ong et al. 2024). Of those patients with intermediate-risk disease, 25% received RT (9% RT + ADT; 16% RT without ADT) (Ong et al. 2024). Based on the projected incidence of prostate cancer in 2024 (n = 26,400), it is estimated that 2,970 patients who have intermediate-risk prostate cancer will receive RT with or without ADT. This number of patients represents the eligible population in this PICO.

PASC noted approximately 1,000 persons may currently be receiving ADT as an adjunct therapy to RT in Australia, based on current population data suggesting 25% of newly diagnosed prostate cancer patients with intermediate-risk disease receive RT (9% with ADT and 16% without).

PASC noted evidence suggesting that large institutional variations exist in the use of ADT with definitive RT, including between public versus private and regional versus metro settings (Ong et al. 2017).

Rationale of the proposed population

The rationale for the ArteraAI Prostate Biopsy Assay is to aid in risk classification and prognosis, and to predict which patients will benefit from hormone therapy to inform management decisions.

For patients with intermediate-risk localised prostate cancer, the ArteraAI Prostate Biopsy Assay (i.e. ADT benefit model) has been developed to help assess whether potential risks from significant adverse events associated with hormone therapy outweigh the clinical benefits (Spratt et al. 2023). Potential adverse effects of ST-ADT include endocrine symptoms (e.g. hot flushes, fatigue), sexual/reproductive dysfunction, osteoporosis, emotional and cognitive changes, and cardiovascular issues (Krauss et al. 2023).

Research from ArteraAI indicated that most patients diagnosed with intermediate-risk localised prostate cancer are unlikely to gain significant clinical advantage from hormone therapy (Application form, p.11 of the PICO Set) (Gerrard et al. 2024; Krauss et al. 2023).

While the ArteraAI Prostate Biopsy Assay can be utilised across all NCCN risk groups, providing assessments of the 10-year risk of distant metastasis and prostate-cancer-specific mortality (ARTERA 2024), this PICO focuses specifically on the intermediate-risk patient subgroup. For this group, the assay is particularly useful in predicting the potential therapeutic benefits of adding ST-ADT to RT. According to the applicant (personal communication, 17 October 2024), the population included in the TGA submission is broader than the population included in this application.

PASC noted that the population included in the TGA submission for the ArteraAI Prostate Biopsy Assay is broader than the population included in this application.

The training and validation studies used in the development of the ArteraAI models are discussed in the Intervention section.

The ASTuTE trial is an ongoing clinical trial on the ArteraAI Prostate Biopsy Assay currently taking place in Australia (Australian and New Zealand Clinical Trials Registry [Internet] 2023). The trial is enrolling adult male patients ≥18 years of age with intermediate-risk localised adenocarcinoma of the prostate, according to NCCN risk stratification, and estimated life expectancy >10 years who are planned for curative-intent RT. Exclusion criteria include insufficient tissue and/or histopathology issues (only formalin-fixed, paraffin-

embedded specimens can be used for testing), histological or cytological evidence of neuroendocrine or small cell differentiation, node positive or presence of distant metastases, absence of histologically proven prostate adenocarcinoma that can be ISUP-graded, and patients who have already commenced ADT.

Compared with the ongoing ASTuTE trial, which requires study participants to have an estimated life expectancy >10 years, the population included in this PICO does not have an explicit life expectancy exclusion. The broader inclusion in the PICO may capture a wider demographic, possibly more accurately reflecting clinical practice and real-world decision-making.

PASC noted that the proposed testing was intended for patients 'planned for curative-intent RT', meaning that eligible patients must have an estimated life expectancy of ≥5 years, in line with NCCN guidelines. PASC noted that the proposed item descriptor does not include any restriction on life expectancy. PASC noted that the ongoing ASTuTE trial requires patients to have an estimated life expectancy of >10 years for inclusion. PASC also noted that while the ASTuTE trial excludes patients who have already commenced ADT and recommends that treatment with ADT does not commence until the result from ArteraAI testing is received in case of a change in recommendation, ADT may begin if deemed clinically necessary. Therefore, some patients may already have commenced ADT before ArteraAI results are known.

Prior tests

Prior to ArteraAI Prostate Biopsy Assay testing, patients are required to undergo conventional diagnostic approaches, including a diagnosis and risk stratification of prostate cancer. These methods, based on histopathology of haematoxylin and eosin (H&E)-stained prostate core needle biopsies, can aid in initial clinical decision-making (Logan et al. 2024); however, they often lack the precision required to accurately capture the aggressiveness of the disease, resulting in uncertainty about the optimal course of treatment (NCCN 2024a).

An essential part of the diagnostic approach involves measuring PSA levels, which—along with clinical T stage and Gleason score—serve as key initial indicators for prostate cancer assessment. Elevated PSA levels often lead to further investigations, including needle biopsies and imaging investigations, to confirm the presence and extent of cancer and to assess its characteristics (NCCN 2024a; Thomsen et al. 2020).

A biopsy is needed to confirm whether prostate cancer is present (NCCN 2024a). According to a local clinician most patients in Australia would undergo a transperineal prostate biopsy in the context of abnormal PSA, digital rectal exam and prostate MRI (personal communication, expert urologist, 30 October 2024). PSA quantitation, needle biopsies and relevant imaging investigations are listed on the MBS for the diagnosis of prostate cancer (Table 12, Appendix).

Biopsy specimens used by the ArteraAI Prostate Biopsy Assay must be treatment-naïve and prepared from H&E-stained formalin-fixed paraffin-embedded (FFPE) tissue (Application form, p.13 of the PICO Set).

Intervention

Description of ArteraAI prostate Biopsy Assay

The ArteraAI Prostate Biopsy Assay is a software-based investigative tool that includes a prognostic model and a predictive model to provide clinical insights for patients with localised prostate cancer. Using WSIs of prostate needle biopsy specimens, the assay analyses tissue morphology and combines these findings with

clinical data including patient age, cancer stage, Gleason score and PSA level (Esteva et al. 2022; Spratt et al. 2023) to provide estimates of:

- prognosis of distant metastasis and prostate cancer-specific mortality (PCSM) after curative-intent RT (regardless of ADT) (Esteva et al. 2022)
- prediction of whether a patient is likely to benefit from addition of ST-ADT to RT (Spratt et al. 2023).

The ArteraAI Prostate Biopsy Assay is not a replacement for any test currently in use, but will provide patients and clinicians with an additional tool to aid their shared decision-making. The assay is not currently funded for any indication in Australia.

Proposed use of ArteraAI Prostate Biopsy Assay

Eligibility

The proposal for public funding is for use of the assay in patients with localised prostate cancer of intermediate risk planning to receive curative-intent RT.

The ArteraAI Prostate Biopsy Assay is advertised to be applicable across all NCCN risk groups for localised prostate cancer (ArteraAI 2024a). The prognostic model can be used in a broader population; however, the current proposal for public funding is limited to those with intermediate-risk disease planning to receive curative-intent RT. The model being proposed for use in Australia was trained on United States (US)-based data from patients who received RT. Its prognostic outputs may not be applicable to patients who do not receive RT. The initial training cohort contained mainly high- and intermediate-risk patients, plus a small percentage of low-risk patients (Spratt et al. 2023). It was noted that these low-risk patients would better suit the intermediate-risk group, due to changes in scoring methods for tumour stage and Gleason score (Spratt et al. 2023). In later versions of the prognostic and predictive models, 3 additional trials (9902, 0415 and 0521) were added (Gerrard et al. 2024): all patients were treated with RT, 2 trials enrolled high-risk patients and 1 enrolled low-risk patients (Lee et al. 2024; Rosenthal et al. 2019; Ross et al. 2024).

The predictive model only provides a report for intermediate-risk patients, classifying them into positive or negative for ST-ADT benefit. This use aligns with the development population, which consisted primarily of intermediate-risk patients who received RT with or without ADT; ADT for patients in the verification subset was limited to ST-ADT only (Spratt et al. 2023)

The treating clinician is to identify eligible patients and order the assay tests.

Specifications

The following specifications are relevant to the proposal for public funding:

- The assay would be used only once in the lifetime of a patient.
- The assay would be ordered by the licensed clinician who treats the patient, principally a urologist, radiation oncologist or medical oncologist.
- The test would be conducted in a pathology laboratory by a qualified histopathologist.
- The assay would be accessed via the ArteraAI web portal, on an ArteraAI server located in Australia, hosted by Amazon cloud service.
- The testing laboratory would need to have one of the 2 approved WSI systems: Philips Ultra Fast or Grundium Ocus®20. (The applicant confirmed that the 2 approved systems are available in some

labs in Australia. For labs without, physical slides could be transported to a central point [personal communication, applicant, 17 October 2024].)

- The laboratory histotechnician would need to be trained in using the WSI system and the ArteraAI biopsy assay. (The applicant advised that most histotechnicans are trained to operate WSI systems and that no training is required for using the ArteraAI web portal and support would be provided [personal communication, applicant, 17 October 2024].)
- A qualified histopathologist would need to review and certify reports produced by the assay (i.e. ensuring that the patient identifier is correct, the patient is in the correct population, and the report meets laboratory standards [personal communication, applicant, 17 October 2024]).

PASC noted that if biopsy specimens have already been digitised, then these same WSIs can be utilised. However, PASC considered that in Australia, most labs do not routinely digitise pathology slides as standard practice. Therefore, PASC considered that the digitisation would reflect an additional step with likely additional costs.

PASC noted that currently only 2 types of scanners have been validated for use by the applicant. Thus, PASC considered that most slides would need to be referred to central laboratories that have one of these scanners. PASC noted that the applicant indicated they intend to expand the number of validated scanners.

PASC noted that in Australia most laboratory histotechnicians are not trained to operate WSI systems. Nevertheless, the applicant has indicated that histotechnicians will be responsible for entering patient clinical information onto the ArteraAI web portal, based on an order form received from the treating clinician, as well as performing the WSI and uploading images to the portal. PASC noted that histotechnicians in Australia are currently not required to hold a degree in science or laboratory medicine. PASC considered that there was the potential for transcription error(s) and mistakes in processing WSIs for the ArteraAI Prostate Biopsy Assay.

PASC noted a pathologist must 'review and certify' the results received from the web portal. PASC queried who carries medicolegal responsibility for the treatment decisions derived from the use of the ArteraAI Prostate Biopsy Assay. PASC noted that the applicant's clinical expert opinion—based on experience from the ASTuTE trial—was that clinicians have accepted they have the final call and responsibility sits with the clinician making the treatment decision (in consultation with the patient).

Clinical involvement

- A treating clinician would identify a patient's eligibility and order the tests from a pathology laboratory equipped with an approved WSI system and ArteraAI access.
- As per current standards of care, eligible patients would have Gleason score results, diagnosis of cancer stage and baseline PSA level. The clinician would complete the order form with patient age, clinical variables and deduced NCCN risk group.
- A histotechnician would prepare WSIs from physical slides, upload to the ArteraAI server along with patient clinical data and conduct the assay.
- The histopathologist would receive the ArteraAI report from the web portal and review and certify the results, then transfer it to the ordering clinician in the appropriate format.
- The clinician would use the report to aid decision-making on whether to add ST-ADT to RT for the patient.

Output

The assay conducts both a prognostic test and a predictive test, generating a report of 10-year risk for prostate cancer metastasis (and other risk assessments) and a binary outcome advising the addition of ADT or not (see sections of sample reports in Figure 1 and Figure 2). The ArteraAI website also provides sample reports, although these differ from the samples provided in the application. Specifically, they include an additional prognostic section for adverse pathology on radical prostatectomy and a clinical interpretation section (ArteraAI 2024b). There are also language changes in the results representation and modifications to the result figures. However, the applicant advised that the website refers to the test offered in the US, and the information available online is not applicable to this application and does not reflect the models offered in Australia (personal communication, applicant, 23 November 2024). The applicant noted that any changes to the model product offered in Australia would be performed in accordance with TGA regulations.

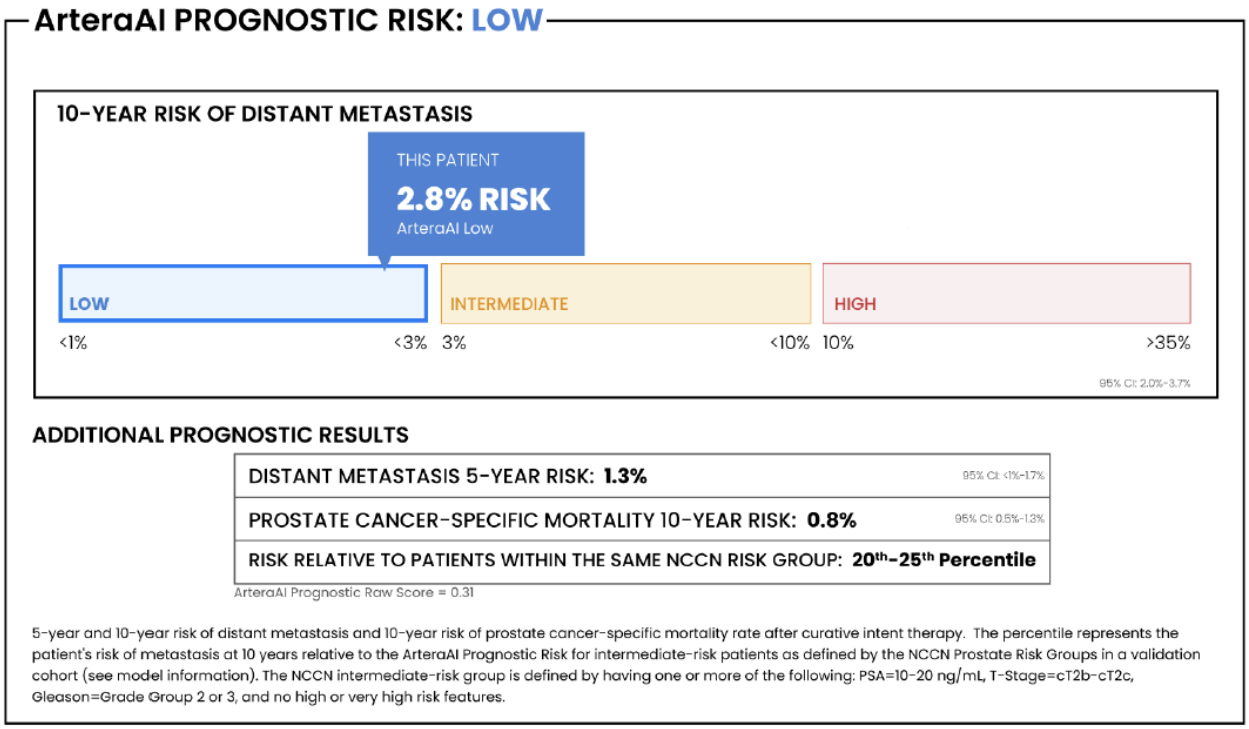
PASC noted that while a range of different outputs are available on the US website (which differ to the examples provided in the application material), the applicant indicated that these are irrelevant to the current application.

The prognostic model of the assay estimates the likelihood (presented as a percentage) of a patient having distant metastasis 10 years after curative treatment and categorises the patient into an ArteraAI risk group of low (<3%), intermediate (3–10%) or high (>10%). All risk rates are reported with 95% confidence intervals (CI).

The 3% threshold was derived from the risk of distant metastasis of NCCN low-risk patients, derived from the ArteraAI internal dataset (personal communication, applicant, 23 October 2024). The 10% threshold was based on the cut-off point suggested in the paper by Spratt and Tward (2020). In that paper, most respondents in the NRG Oncology Genitourinary Committee felt that a 5% absolute risk reduction was an appropriate threshold at which treatment intensification with ADT may be considered appropriate. The applicant advised that 10% was selected as the threshold because, based on a relative treatment effect (hazard ratio) of around 0.5 for ST-ADT when added to RT, a ≥5% risk reduction will occur only in patients with a baseline risk of metastasis of ≥10% (personal communication, applicant, 23 October 2024).

The example test report provided in the application showed additional prognostic information for distant metastasis at 5 years (Figure 1). A prognostic AI raw score and the percentile of the patient's 10-year metastasis risk within their NCCN risk group was also provided (Figure 1).

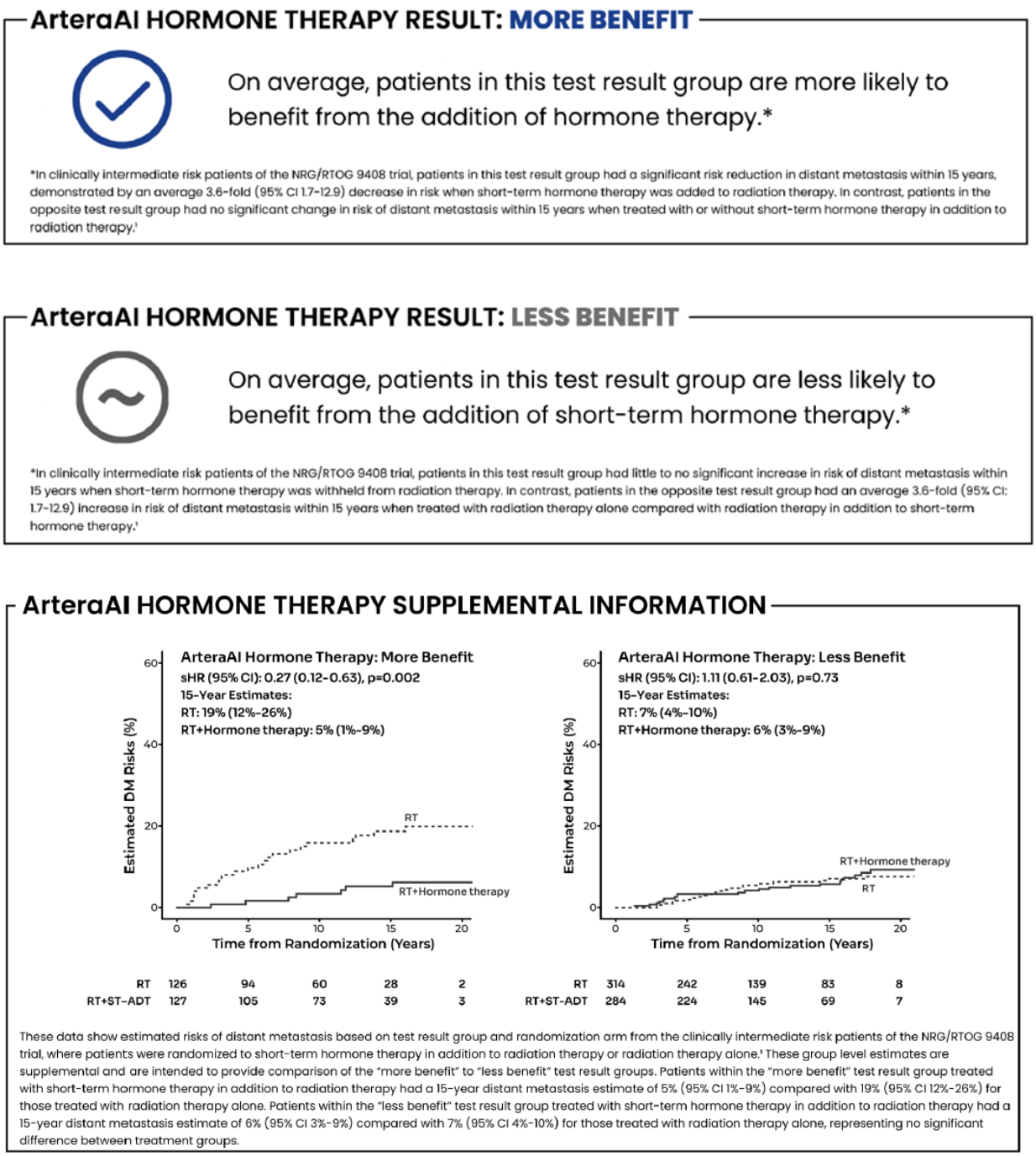
Figure 1 Sample AI report of prognostic model extracted from PICO application set



Source: Application form, Figure 5, p.16 of the PICO Set

The predictive model reports a binary output based on the possibility of additional ST-ADT reducing the risk of distant metastasis in 15 years. The result is either positive or negative in terms of the likelihood of benefit from additional ST-ADT. The sample report provided in the application labelled the result as either more benefit or less benefit (Figure 2). The term 'biomarker' is used in several publications when describing the result of the predictive model. However, considering the definition of a biomarker used within the MSAC guidelines (Department of Health and Aged Care 2021), the model output is referred to as a 'test result' not a 'biomarker' throughout this PICO.

Figure 2 Sample AI report of predictive model extracted from PICO application set



Source: Application form, Figure 7, p.17 of the PICO Set

The results for test-result positive and negative groups in the test data are provided in the sample reports. The test-result positive group shows significantly reduced risk of distant metastasis if treated with ST-ADT relative to receiving RT alone, while no significant benefit (in terms of risk of distant metastases) is seen in the test-result negative group (Figure 2).

Clinical interpretation of tests results

The prognostic model was originally trained and verified on datasets in which all patients had received RT; some patients received additional ADT (of various treatment periods) (Spratt et al. 2023). The additional 3

trials used in the development of subsequent versions of the model (trials 0415, 0521, 9902) (Gerrard et al. 2024; Lee et al. 2024; Rosenthal et al. 2019; Ross et al. 2024) also included patients treated with RT. Prognosis of risk was based on the event of distant metastasis and PCSM in the follow-up data of those patients (Esteva et al. 2022; Gerrard et al. 2024). Therefore, the estimated probability (low/intermediate/high) of a patient's risk of distant metastases or PCSM is based on the assumption that the patient received RT.

Being categorised into an AI low-risk group can be interpreted as the patient's risk of distant metastasis being <3%, if treated with RT. Being categorised into an AI high-risk group means the risk is >10%, even with RT treatment.

The binary result of the predictive model is presented as an average finding (Figure 2). Based on results from the validation cohort, patients in the test-result positive group had a significantly reduced risk of distant metastasis if treated with ST-ADT in addition to RT relative to RT alone, while patients in the test-result negative group had no significant benefit (Figure 2).

Both the prognostic and predictive test results are used for clinical decision-making, meaning the results are used in combination (the results from the models are included in the same report). The clinician would value both sources of information when choosing to recommend ST-ADT for a patient or not (personal communication, applicant, 29 November 2024).

PASC noted the proposed tool includes 2 models: a prognostic model and a predictive model. PASC queried how the addition of the prognostic model may affect treatment decision-making and whether it was necessary for the decision-making context. Input from the applicant's clinical experts was that the prognostic and predictive aspects of the model are complementary tools and considered together. PASC noted that in the applicant's reporting of early observations from the ASTuTE trial, many patients showed a low absolute risk for distant metastasis. PASC considered that even if the predictive biomarker was positive, the absolute benefit of ADT would be low, given the low absolute risk of distant metastases. Overall, PASC noted that the absolute risk data from the prognostic model and the relative risk reduction benefit achieved through addition of ADT suggested by the predictive model, are complementary pieces of information and the relative benefit needs to be considered in the context of the absolute risk.

PASC questioned if the ArteraAI algorithm prognostic result could lead to a complete re-evaluation of the proposed main treatment (e.g. a switch from RT to active surveillance if low risk). PASC noted input from the applicant's clinical expert who advised that the test result would not lead to a change of the main treatment option, adding this is supported by what has been observed to date in the ASTuTE trial.

Claimed Benefits

The predictive model is claimed to assist clinician and patient decision-making in the target population by identifying those likely to benefit from added ST-ADT and those not, thereby increasing treatment effectiveness and reducing unnecessary treatment and harmful side effects.

It is important to note that the test-result positive and negative groups only differed with respect to risk of distant metastasis and PCSM. There was no difference between groups in terms of overall survival and metastasis-free survival. Spratt et al. (2023) suggested that this may be explained by the fact that a large percentage of observed death events were not caused by prostate cancer and many follow-ups ended before distant metastasis occurred (Spratt et al. 2023). However, it was not explored what proportion of

deaths could be treatment-related, or if there were differences in ADT-related side effects between groups. Genetic mutations/variants have been reported to be associated with both ADT response (Shiota et al. 2019) and ADT induced symptoms (Karunasinghe et al. 2016). It is possible that the patients who responded well to ADT did so because their whole-body tissues are genetically predisposed to be sensitive to hormone depletion. These patients may also suffer greater side effects compared to the test-result negative group, which could lead to higher risk of treatment-related death.

It is claimed that the prognostic model provides a more accurate prognosis than NCCN guidelines. Considering the characteristics of the populations used for model development, prognostic information provided by the ArteraAI Prostate Biopsy Assay may only be applicable to patients treated with RT (see Clinical interpretation of tests results).

The ArteraAI Prostate Biopsy Assay has no direct negative impact on patient health, as the required inputs for the tests are either already collected or ready to be produced from pre-collected data and samples.

Algorithms of the assay

The terms 'model' and 'algorithm' are often used interchangeably. To prevent confusion, the term 'model' is used for the algorithms of the assay from the user's point of view, and the term 'algorithm' is used for the mathematical models underlying the surface of the 2 models.

The ArteraAI Prostate Biopsy Assay prognostic and predictive models were trained and validated independently but share many similarities:

- Both models used the same randomised clinical trials (US-based) for their data sources, including only patients with high-quality WSIs. At least in the earlier versions, the included samples were mainly high-risk and intermediate-risk, with a small proportion of low-risk patients that were close to the intermediate-risk criteria (Spratt et al. 2023).
- Both models used self-supervised learning and layered neural network methods (Esteva et al. 2022; Gerrard et al. 2024; Spratt et al. 2023).
- Both models were developed with a standalone validation dataset not overlapping with the training dataset (Esteva et al. 2022; Gerrard et al. 2024; Spratt et al. 2023).
- Both models were trained on images first, then the output of the image-learning algorithm was combined with the clinical variables and trained towards the endpoint (e.g. distant metastasis) of the relative model (Esteva et al. 2022; Spratt et al. 2023).
- Both models included age, base PSA level and tumour stage (Gerrard et al. 2024) in their clinical variables; however, the predictive model version currently being proposed for use in Australia also includes combined Gleason score, Gleason primary score and Gleason secondary score (Table 7).

The prognostic model included all eligible patients. A larger portion of samples from each trial was used as a training dataset and the leftover smaller portion as a validation dataset.

The predictive model kept one randomised trial (RTOG9408) for validation, which contained patients with localised prostate cancer who received RT plus ADT or RT only (Spratt et al. 2023). These patients were of intermediate risk or close to. The remaining trials were used to train image algorithms; however, only trials containing mainly intermediate-risk patients were used for downstream predictive training (i.e. training the algorithms, taking image algorithms as outputs and clinical variables as inputs).

PASC noted this is the first application to MSAC requesting list of an AI algorithm involving digitised pathology images.

PASC noted there are 2 separate machine learning pipelines, including 1 for pathological image analysis and 1 for joint clinician and image data analysis.

PASC questioned whether the algorithm was only trained on core biopsies, or also on TURP (transurethral resection of the prostate) chips. PASC considered that core needle biopsy must be stipulated as a sample requirement in the proposed MBS item descriptor, and other histology samples should be excluded.

The algorithms of the ArteraAI Prostate Biopsy Assay have had several version updates (Esteva et al. 2022; Gerrard et al. 2024; Ross et al. 2024; Spratt et al. 2023). The varied descriptions show changes made to trial datasets in development of the model (both training and validation), sample selection, training validation dataset splitting methods, model inputs and possibly model design.

The applicant provided information to clarify the versions of both models being proposed for listing on the ARTG (personal communication, applicant, 23 October 2024) (Table 7). Nevertheless, this application is requesting consideration of the assay's algorithms more generally, regardless of version changes.

PASC noted the proposed algorithms for Australia are 'locked' rather than continually learning; however, when there is an appropriate amount of additional information, Artera may update the algorithms. PASC considered it unclear how newer updated evidence might relate to the specific versions of the ArteraAI algorithm being proposed for use in Australia, including any impact on subsequent changes to the algorithm.

Table 7 ArteraAI Prostate Biopsy Assay versions as provided by applicant

Model	Version in Artera's submission to TGA	Variables included	Publication supporting results
Prognostic model	1.2	Age PSA Tumour stage	Gerrard 2024
ST-ADT (predictive) model	1.2	Age PSA Tumour stage Gleason score	Spratt 2023

PSA = prostate specific antigen, ST-ADT = short-term androgen deprivation therapy, TGA = Therapeutic Goods Administration
Source: table provided by the applicant (personal communication, applicant, 23 October 2024).

The supporting publication of the ST-ADT (predictive) model included in the TGA submission is based on an earlier version including Gleason score. It is noted that Gerrard et al. (2024) described both the prognostic and predictive models, while only the prognostic model validated in this study was included in the TGA submission. Importantly, Gerrard et al. (2024) stated that Gleason scores had been removed from both models (Gerrard et al. 2024). The authors also described changes in clinical trials used in the development process. Specifically, they included 3 additional trials not presented in Spratt et al. (2023). One of these trials (RTOG9902) was used for external validation of an earlier version of the model (Ross et al. 2024). This trial contained mainly high-risk patients. The figures included for the predictive model in the sample report currently available on the ArteraAI website, (ArteraAI 2024b) aligns with Gerrard et al. (2024). This

highlights the potential for future updates or revisions and indicates that not all available evidence may be relevant to the iteration submitted to the TGA. The application should clearly specify which iterations of the algorithm the included data corresponds to. The application may also need to identify change in the algorithm's predictions over time by presenting results for the same datasets across different iterations.

A comparison of the major differences between these papers is presented in Table 8, along with accompanying information from the study by Esteva et al. (2022). None of the papers provided model version numbers.

Table 8 ArteraAI Prostate Biopsy Assay models as described in publications

	Esteva 2022	**Spratt 2023**	**Gerrard 2024**
Model	Prognostic	Predictive	Prognostic and predictive
Gleason scores	Included	Included	Not included
Trials included	5 trials: 9202, 9408, 9413, 9910, 0126	5 trials: same as those included in Esteva 2022	8 trials: same 5 trials included in Esteva 2002 plus 3 additional trials: 0415, 0521, 9902
Total patients included (n)	5,654	5,688	7,026
Dataset split	Training: 80% Validation: 20%	Training for image: trials 9202, 9408, 9413, 9910 Training for prediction: trials 9910, 0126 Validation: trial 9408	Validation: trial 9408 Other details not specified
Training dataset (n)	4,523*	2,024	Prognostic: 5,259 Predictive: 3,977
Validation dataset (n)	Initial: 1,131*, then 931	1,594	Prognostic: 1,767 Predictive: 1,509

Note: *Calculated by the assessment group based on the reported percentages.

Generalisability considerations

- Generalisability of the developing dataset to the target population
  The training and validation process was repeated on most of the involved datasets multiple times. Validation sets appear to have been later incorporated into model development, raising concerns about potentially biased model performance estimates. It is uncertain if the results can be generalised to the broader target population from those samples. External validation is needed to confirm the effectiveness of the assay. Currently, only one previous version of the prognostic model has been externally validated, with a small sample size. The trial used for the validation was then used in the development of the current version.
- Generalisability to the Australian population
  The assay was developed with a population containing Europeans and a reasonable proportion of African descendants (<5% other ethnic groups). The model may not be generalisable to patients other than those with European or African ancestry. Australia has a different racial profile, which

may raise concerns of applicability, including with respect to disadvantaged ethnic groups not represented within the training and validation datasets of the assay.

- Generalisability to different scanners
  Imaging features can be affected by factors relevant to the devices, instead of to the disease or the patient. Gerrard et al. (2024) emphasised that each scanner model must be individually validated. The authors reported validation test reliabilities with scanner model 3DHistech P1000; however, the sample sizes were small (30 cases in each group). Validation of the 2 approved scanners is not found in published papers.

PASC noted the ArteraAI Prostate Biopsy Assay was developed, trained and validated based on retrospective analyses of digital pathology images from pretreatment prostate tissue and clinical data from US randomised trials. PASC questioned whether the currently available data in the algorithm is likely to be reflective of performance in an Australian patient cohort. Clinical opinion shared during the meeting was that while there may be potential nuances between the development cohorts and the Australian population, the biology of the disease and its underlying mutations are similar across continents, suggesting applicability of the development data may not be of significant concern.

PASC noted the models were originally trained and verified on datasets in which all patients had received RT, implying prognostic information derived from the assay may only be applicable to patients treated with RT. PASC suggested it will need to be considered whether current trials relating to external beam radiation therapy can be extrapolated to patients planned for brachytherapy.

PASC noted concerns in terms of scanner variation, as well as variation in tissue preparation and staining between laboratories.

Comparator(s)

The application proposed that the current standard of care, guided by NCCN and EAU guidelines for risk assessment in localised prostate cancer, serves as the appropriate comparator to the ArteraAI Prostate Biopsy Assay.

According to the application, there are no other prognostic classifier tests or tests predicting response to hormone therapy registered for use in Australia (MSAC Application form, pp 19–20 of the PICO Set). Therefore, the standard decision-making process without the ArteraAI Prostate Biopsy Assay, which relies on NCCN and EAU guidelines to inform treatment decisions including use/non-use of ST-ADT, is proposed as the comparator. The ArteraAI Prostate Biopsy Assay is positioned as an add-on to this established standard of care.

According to NCCN guidelines, only patients with unfavourable risk and with a ≥5-year life expectancy are indicated for combined RT and ADT; in other groups, additional ADT is optional, with detailed guidance provided in the guidelines (NCCN 2024b).

Current Practice

The NCCN guideline risk groups have prognostic value and are commonly used for guiding patient treatment; however, heterogeneity in prognosis exists within each risk group (Schaeffer et al. 2024). Zelic et al. (2020) compared the prognostic performance of various pretreatment risk stratification tools for prostate cancer and found risk grouping systems such as those of the EAU and NCCN performed similarly

(Zelic et al. 2020). Some other systems were shown to outperform the NCCN and EAU risk groupings, including the Cambridge Prognostic Groups risk grouping system, the Cancer of the Prostate Risk Assessment score and the Memorial Sloan Kettering Cancer Center nomogram, which all performed better in discriminating PCSM (Zelic et al. 2020). Nevertheless, according to the application, the standard systems used in Australia are the NCCN (used by radiation and medical oncologists) and the EAU (endorsed by urologists) classification systems (Application form, p.3 of the PICO Set), making these the most relevant comparators.

NCCN guidelines indicate that certain germline mutations are associated with more aggressive prostate cancer and a poorer prognosis, although these are not generally considered for risk stratification (Schaeffer et al. 2024). According to the guidelines, common histopathology variables (e.g. cribriform histology, intraductal carcinoma, % Gleason pattern 4) and clinical variables (e.g. PSA density) are also prognostic (Schaeffer et al. 2024).

Clinical advice indicates that the volume of disease and the number of adverse pathological factors such as presence of cribriform pattern disease or >10–20% pattern 4 disease, as well as patient life expectancy, presence of comorbidities, bladder function and personal preference may all be taken into account when making treatment decisions for patients with localised intermediate-risk disease (personal communication, expert urologist, 30 October 2024).

PASC noted the proposed comparator is current standard care using NCCN or EAU risk stratification tools. According to NCCN guidelines, patients with unfavourable intermediate-risk prostate cancer and >5 years life expectancy are indicated for RT + ADT. In other groups, the addition of ADT is suggested only if additional risk assessments suggest aggressive behaviour. PASC acknowledged that the NCCN guidelines refer to a range of other risk assessment tools (including molecular assays) and indicate that certain histological features (cribiform histology, intraductal carcinoma, % Gleason pattern 4) are prognostic. PASC noted that it remains unclear to what extent Australian clinicians are considering these additional NCCN-suggested factors in risk stratification and whether they should be considered to form part of NCCN risk stratification.

PASC noted that other risk stratification tools (e.g. Cambridge Prognostic Groups, Memorial Sloan Kettering nomogram) have been shown to outperform EAU and NCCN risk groups at predicting PCSM.

PASC acknowledged that there is no single agreed-upon predictive tool used in Australia, making the relevant guidelines the most appropriate comparators.

PASC noted that in comparing the ArteraAI predictions to NCCN risk stratification, the ArteraAI predictions should be compared to the NCCN favourable and unfavourable intermediate-risk groups separately.

Additional comparators

In its most recent guideline update, the NCCN explored advanced multivariable risk stratification models (Schaeffer et al. 2024). The guideline identified literature published on 3 gene-panel tests—the 22-gene genomic classifier assay (Decipher), the 31-cell cycle progression gene assay (Prolaris) and the 17-gene assay Genomic Prostate Score assay—along with the ArteraAI Prostate Biopsy Assay. All 3 gene-panel tests provide prognostic information that can be used to stratify patients into risk groups (Schaeffer et al. 2024). These are all potential comparators for the ArteraAI prognostic model.

The NCCN guidelines also explored the potential treatment implications for tools with Simon level IB evidence,[4] including the Decipher genomic classifier assay and the ArteraAI Prostate Biopsy Assay (Schaeffer et al. 2024). According to the guidelines, Decipher scores can also be used to aid decisions on whether to add ST-ADT to RT. For patients with NCCN intermediate-risk disease, RT alone can be considered for those with a low score, while RT with ST-ADT can be considered for those with a high score. Therefore, Decipher is also a suitable comparator for the ArteraAI predictive model.

None of these tests are currently registered for use in Australia or reimbursed under the MBS.

PASC noted there are no other tests predicting response to hormone therapy that are registered for use in Australia, although there are multiple stratification tools available and mentioned in NCCN guidelines. In particular, PASC recognised that the Decipher 22-gene genomic classifier, which has predictive features, may be a relevant secondary comparator.

Another potential comparator prognostic tool is the PREDICT Prostate tool, a web-based clinical decision support tool recommended by the EAU and endorsed by the National Institute of Health and Care Excellence (Cornford et al. 2024; National Institute of Health and Care Excellence 2021). The tool estimates the relative advantage of active versus conservative treatment and death from any cause at 10 and 15 years. It is a multivariable model developed and validated (70:30 ratio) with a large sample (n = 10,089) with 9.8 years median follow-up (3,829 deaths including 1,202 prostate cancer specific deaths) (Thurtle et al. 2019). The model—externally validated in a small Singapore cohort (n = 2,546) and a larger Swedish cohort (n = 69,206)—demonstrated good generalisability across ethnicity and healthcare systems (Thurtle et al. 2020; Thurtle et al. 2019). However, the PREDICT Prostate tool does not predict the effect of ADT treatment.

PREDICT Prostate is a free, online clinical decision-making support tool that uses only clinical data (i.e. it does not directly process or analyse a medical image or signal from another medical device) and is therefore exempted from ARTG listing (TGA 2021).

PASC noted another potential comparator, the PREDICT Prostate tool, which is a free web-based clinical decision-making support tool endorsed by the EAU, but acknowledged that this tool does not predict response to ADT. PASC noted advice from the applicant indicating that, according to their nominated experts, it is not widely used in Australia.

Reference standard

The ArteraAI Prostate Biopsy Assay is performed for the purpose of determining a future health outcome (prognostic/predictive). In such instances, the reference standard for assessing the accuracy of the prediction is the health outcome of interest at a later timepoint (Department of Health and Aged Care 2021).

The prognostic algorithms predict future outcomes, including 10-year risk of distant metastasis and 10-year risk of PCSM. In this instance, the reference standard could be the rate of development of distant metastasis (at 10 years) or the rate of PCSM (at 10 years), respectively. By way of example, in the evaluation of the prognostic performance of EndoPredict® (MSAC Applications 1408 and 1408.1), late

[4] Simon 2009 developed a revised hierarchal levels of evidence scale for tumor marker studies (Simon, Paik & Hayes 2009). Simon Level 1 B evidence is considered when one or more validation studies with consistent results are available.

distant recurrence was used as an evidentiary (reference) standard (Medical Services Advisory Committee 2019).

The predictive algorithm predicts the likelihood that patients would benefit from the use of ST-ADT by classification of test results as positive or negative. Here, the reference standard could be whether test-result positive and negative patients respond differently to the addition of ST-ADT as an adjunct therapy versus RT alone.

PASC noted the proposed reference standards for assessing the accuracy of the ArteraAI Prostate Biopsy Assay's prognostic and predictive outputs are the health outcomes of interest at a later timepoint. PASC queried the difference between the reference standard and the question for assessment.

Outcomes

Because the proposed test produces 2 outputs (predictive and prognostic), the outcomes associated with test accuracy must be assessed individually. However, changes in clinical management and treatment decisions are based on the combined results of both test outputs. Other outcomes, including change in management and patient health outcomes apply more generally across both models and have not been separated.

Effectiveness outcomes

Test accuracy of the predictive model

- Test reliability: inter- and intra-operator reliability; inter- and intra-scanner reliability (e.g. per cent agreement)
- Predictive accuracy (with reference to response to treatment in test-result positive and negative patients)

Test accuracy of the prognostic model

- Test reliability: inter- and intra-operator reliability; inter- and intra-scanner reliability (e.g. using an intraclass coefficient)
- Longitudinal accuracy (with reference to a health outcome of interest [distant metastasis, PCSM] at a later timepoint e.g. using area under the curve for time-dependent receiver operator characteristics of sensitivity and specificity)

Comparative effectiveness in selecting patients for RT + ST-ADT treatment

Change in clinical management

- Change in the proportion of patients referred for or treated with RT + ST-ADT or RT alone

Patient-centred health outcomes

- Change in overall survival
- Change in prostate cancer-specific survival
- Change in occurrence of distant metastases
- Change in biochemical failure/recurrence (increasing PSA) defined by the Phoenix definition of nadir +2 ng/mL (blood PSA measurement)
- Change in patient-reported health status (e.g. Expanded Prostate Cancer Index Composite [EPIC-26]/quality of life [QoL])

Safety outcomes

- Adverse events of treatment with ST-ADT
- Harms (psychological health risks) associated with testing

Value of knowing

- Knowledge of prognosis for future planning/patient decisions

Healthcare system outcomes

- Costs associated with the ArteraAI Prostate Biopsy Assay (in addition to standard care)
- Costs of treatments received/cost offsets from avoidance of ST-ADT
- Costs associated with the management of ST-ADT-related adverse events
- Cost-effectiveness

PASC noted the proposal that the test accuracy outcomes of the predictive and prognostic models must be assessed individually. PASC noted that the clinician would then receive the 2 test outputs in combination, integrating the predictive and prognostic model outcomes to inform treatment decisions (in consultation with the patient). Therefore, PASC considered that any change in clinical management and treatment decisions is based on the combined results of both test outcomes.

Rationale for selected outcomes

The International Consortium for Health Outcomes Measurement (ICHOM) has developed a standard set of patient-centred health outcome measures for evaluation of localised prostate cancer treatment outcomes (Martin et al. 2015). The health outcome measures proposed for the PICO capture those proposed by ICHOM, including overall survival, prostate cancer specific survival, distant metastasis, biochemical failure/recurrence and patient-reported health status. QoL is also included in the PICO.

Biochemical recurrence occurs when there is a significant increase in PSA levels post-treatment. The Phoenix Consensus Conference 2005 (sponsored by the Radiation Therapy Oncology Group/American Society for Therapeutic Radiology and Oncology) proposed a PSA increase of 2 ng/ml or more above the PSA nadir as a standard definition for biochemical recurrence, regardless of the nadir value (Roach et al. 2006; Van den Broeck et al. 2020).

Many patient-reported outcome measures (PROMs) tools exist. ICHOM recommends using the EPIC-26, which asks patients to report on domains related to urinary, bowel, sexual and hormonal symptoms (Martin et al. 2015). In addition to the EPIC-26, ICHOM notes that a general QoL measurement tool may be used if desired (e.g. the EuroQOL 5-dimension questionnaire [EQ-5D] or the 12-item Short Form Health Survey [SF-12]) (Martin et al. 2015). ICHOM did not include measurement of general health-related QoL as an essential component of its outcome set but it is included in the PICO outcome set as a patient-relevant outcome.

According to the application, the information provided by the prognostic test improves the value of knowing for patients. Value of knowing includes any consequences affecting the wellbeing of patients—and often family members—beyond the changes in health outcomes. Value of knowing can enable patients to engage in better long-term planning around career, finances and family; provide a greater sense of control over their own medical decisions; and enable a greater understanding of likely future healthcare needs (Department of Health and Aged Care 2021).

Available/upcoming clinical evidence

In the ongoing ASTuTE trial taking place in Australia, the key primary outcome is any change in treatment decisions/clinical management regarding the decision to use/not use ST-ADT in addition to RT before and after receiving the ArteraAI Prostate Biopsy Assay results (Australian and New Zealand Clinical Trials Registry [Internet] 2023). Secondary outcomes of interest include comparison of pre- and post-test costs, including but not limited to testing and treatment-related costs. Biochemical disease control at 5 years will also be assessed using the Phoenix definition of nadir + 2 ng/mL PSA measurement.

As of 4 April 2024, the ASTuTE trial had recruited 29 participants (target of 800 participants) since 8 December 2023 (date of first participant enrolment). Anticipated dates for the last participant enrolment and last data collection are 1 June 2025 and 1 June 2030, respectively (Australian and New Zealand Clinical Trials Registry [Internet] 2023).

PASC noted that the ASTuTE study protocol indicates a subgroup of 100 patients would have their PSA checked at 5 years to assess biochemical disease control. PASC observed that this appears to be the only planned clinical outcome measure. The applicant reported that they are currently engaging with the Prostate Cancer Registry, with the hope of obtaining more complete outcome data later down the track (e.g. linking with Registry data at the 5-year time point). The applicant confirmed that shared decision-making outcomes (preliminary results were noted by PASC, as described above) would be available in time for the applicant-developed assessment report (ADAR), but that downstream health outcomes data would not.

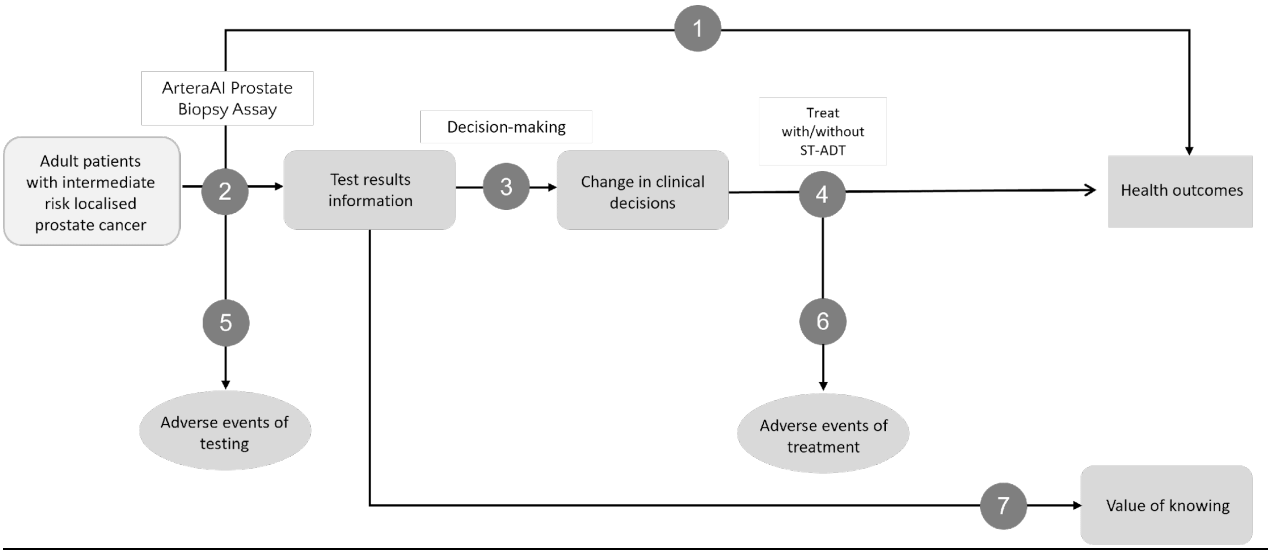
Assessment framework

As the application has made a claim of superiority, the assessment must show an improvement in health outcomes. Results of the ArteraAI Prostate Biopsy Assay could lead to a change in treatment (with/without ST-ADT) for patients likely to benefit or not benefit, which would impact health and clinical outcomes for the patient. The assay may also impact value of knowing outcomes for patients.

In circumstances where direct evidence is unavailable, evidence must be provided at each step of the assessment framework. Figure 3 shows the research questions that need assessing at each step to assess the ArteraAI Prostate Biopsy Assay. Each number within the framework corresponds to one or more research questions that must be answered to support the clinical claim.

PASC considered that a linked evidence approach was appropriate.

Figure 3 Assessment framework



Notes: 1 = direct from test to health outcomes evidence, 2 = test accuracy, 3 = change in diagnosis/treatment/management, 4 = influence of the change in management on health outcomes, 5 = adverse events due to testing, 6 = adverse events due to treatment, 7 = value of knowing test information and its impact on non-health outcomes

Direct evidence

1. Does the additional use of the ArteraAI Prostate Biopsy Assay versus no ArteraAI Prostate Biopsy Assay in patients with intermediate-risk localised prostate cancer planned for curative RT, result in superior improvements in health outcomes (e.g. longer survival, reduced occurrence of distant metastases or biochemical failure/recurrence) and better patient QoL?

Indirect evidence

2.
    a. How does the information provided by the ArteraAI Prostate Biopsy Assay differ from that provided by standard care?
    b. What is the prognostic accuracy of the ArteraAI Prostate Biopsy Assay against a relevant reference standard (health outcome of interest at a later timepoint) compared to risk stratification tools currently used in Australia (e.g. NCCN or EAU risk groups)?
    c. What is the predictive accuracy of the ArteraAI Prostate Biopsy Assay (against a relevant reference standard) compared to current Australian clinical practice?
3. Does the availability of the information provided by the ArteraAI Prostate Biopsy Assay lead to a change in patient management when compared to information gained from standard care/currently used risk stratification tools?
4. What impact does treatment with ST-ADT in addition to RT have on patient health outcomes relative to treatment with RT alone, based on the results of the ArteraAI Prostate Biopsy Assay?
5. What are the physical and psychological health risks associated with the addition of the ArteraAI Prostate Biopsy Assay as an add-on test compared to standard care?
6. Are there differences in adverse health events associated with the use or non-use of ST-ADT based on the results of the ArteraAI Prostate Biopsy Assay compared to standard care?

7. What benefits (or harms) does the availability of information provided by the ArteraAI Prostate Biopsy Assay have on non-health outcomes related to the value of knowing, compared to information provided by standard care?

The above evidence must be provided for both the prognostic model and the predictive model.

Additionally, regarding assessment of predictive value, in previous consideration of a predictive test in breast cancer (MSAC Application 1408.1), MSAC did not accept that predictive value had been demonstrated in the absence of results from prospective studies (e.g. effect modification in an RCT) (Medical Services Advisory Committee 2022). In the context of gene expression profiling (GEP) tests in early breast cancer, MSAC previously advised (MSAC Application 1408) that in the absence of RCT evidence demonstrating predictive value, any future application would need to provide evidence that it meets the following parameters (Medical Services Advisory Committee 2021):

- an appropriate regulatory and quality assurance framework
- an appropriate nomination of clinical place aligned with sufficiently robust clinical evidence of incremental prognostic value
- an adequate justification of cost per test
- an acceptable total net financial cost to government.

Clinical management algorithms

Current clinical management for targeted population

In patients suspected of prostate cancer, diagnosis will be confirmed by core needle biopsy or occasionally incidentally by biopsy of surgically extracted tissue (personal communication, expert urologist, 30 October 2024). If cancer is diagnosed, clinicians will discuss with patients and consider treatment options. Patients with localised prostate cancer are stratified into risk groups per NCCN or EAU guidelines (treatments are recommended in the guidelines for each group, see Management of localised prostate cancer of intermediate risk section). Treatment plans will be established through a shared decision-making process. Both the NCCN and EAU risk groups categorise patients based on clinical factors such as Gleason score, PSA level and clinical stage. Neither provides a direct assessment or estimate of the 10-year risk of distant metastasis.

For patients in the intermediate-risk group, the main treatment options include radical prostatectomy, external beam RT (may be combined with ADT), active surveillance and watchful waiting. Treatment choice is made with consideration of multiple factors such as volume of disease, adverse pathological factors, patient life expectancy, comorbidities, bladder function and patient preference (personal communication, expert urologist, 30 October 2024). For patients with RT planned, the decision on whether to add ADT is largely determined by the radiation oncologist.

Local expert advice included in the application indicated that adjuvant ADT is more likely used in those with high-risk localised cancer, whereas in those with intermediate-risk localised prostate cancer undergoing RT with curative intent, a decision regarding the benefit to risk ratio of ST-ADT is made (Application form, p.5 of the PICO Set).

Initial treatment options for patients with intermediate-risk disease as outlined in NCCN guidelines, guided by risk groups and life expectancy estimates, are illustrated in Figure 4. NCCN guidelines also recommend the use of nomograms to guide decisions (NCCN 2024b). Regarding the use of ADT in addition to definitive RT, the guidelines state that ADT is not routinely used in favourable intermediate-risk disease unless additional risk assessments suggest aggressive tumour behaviour. For unfavourable intermediate-risk disease, the guidelines suggest ADT should be used unless additional risk assessments suggest less aggressive tumour behaviour or if medically contraindicated (NCCN 2024b). EAU guideline recommendations (detailed in Management of localised prostate cancer of intermediate risk) refer to NCCN favourable and unfavourable risk groupings when making recommendations.

Current clinical practice is also reflected in the combined clinical management algorithm (Figure 5), with the proposed intervention included as an add-on to standard care.

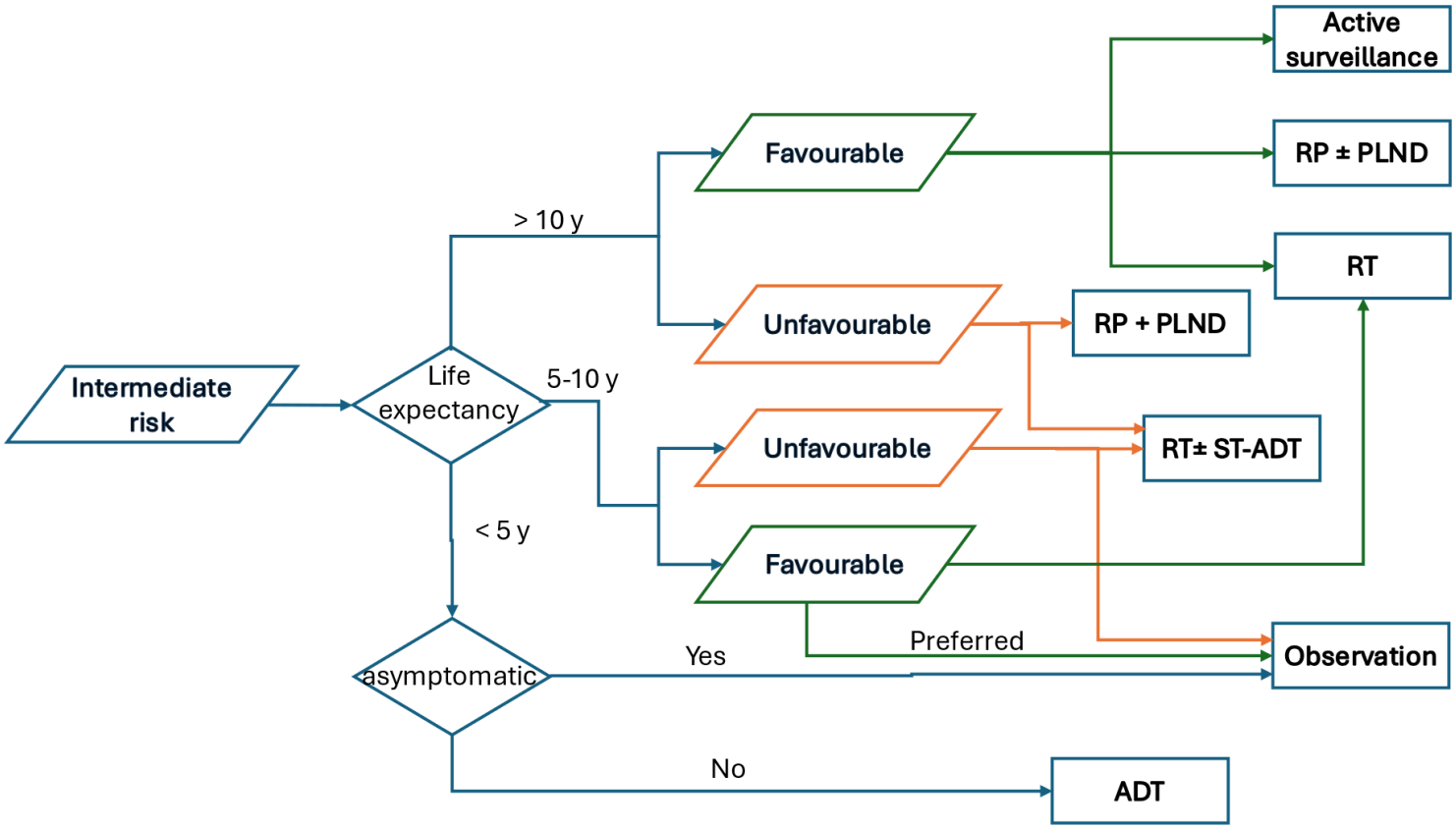
PASC highlighted the importance of life expectancy in the current clinical management algorithm for informing recommended treatment options.

Proposed clinical management for targeted population

ArteraAI Prostate Biopsy Assay is proposed as an add-on test to current risk assessment tools and clinical assessments. For the proposed indication, the ArteraAI Prostate Biopsy Assay is intended to be used after RT is planned, to provide additional information to inform decision-making, mainly regarding whether ADT should be added (Figure 5).

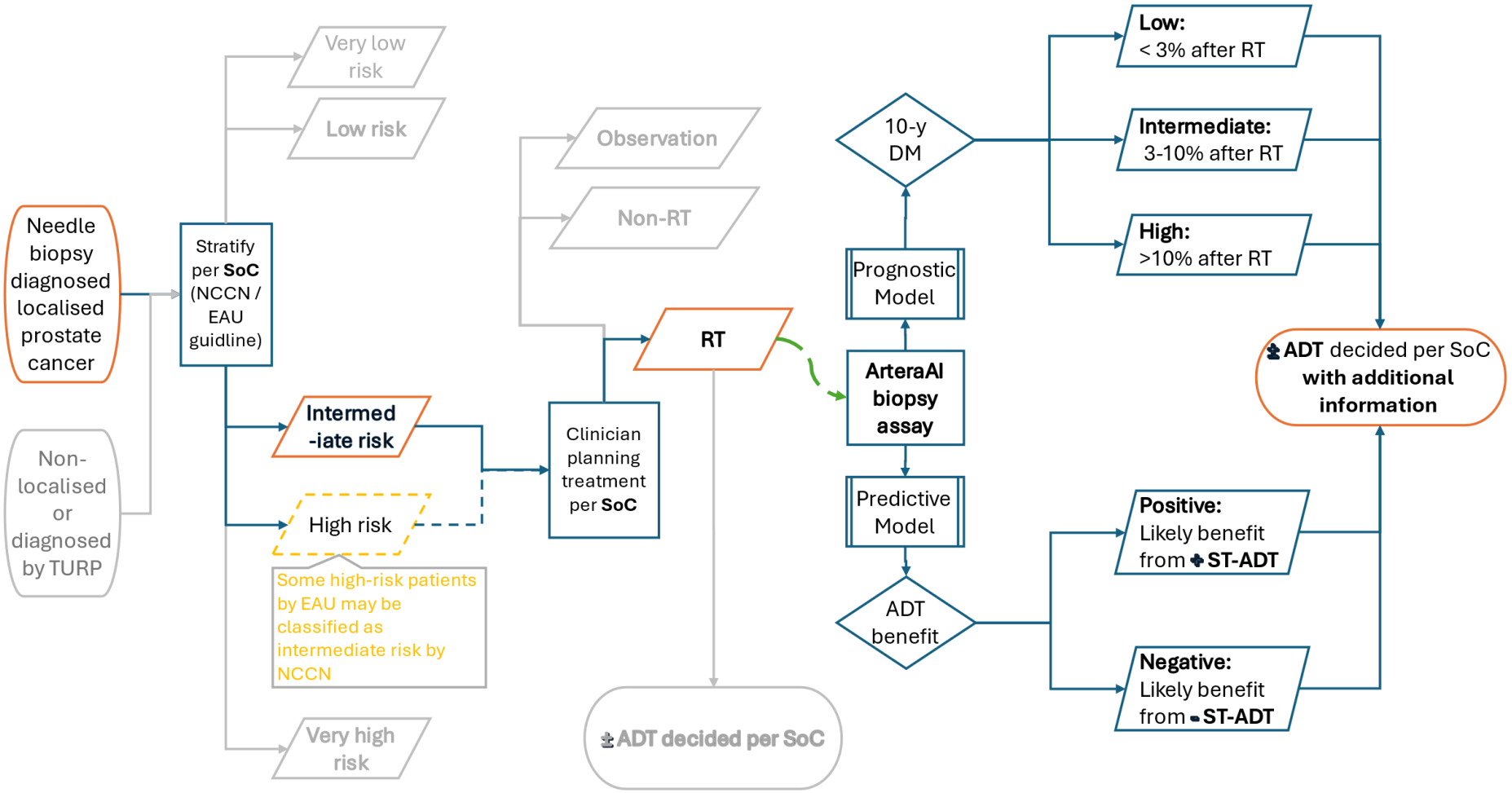
The predictive model has a straightforward application, as it provides a prediction of whether the patient is likely to benefit from the addition of ADT. The results of the prognostic model, although not ADT specific, may provide additional insight. Both the prognostic and predictive test results are used for clinical decision-making, meaning the results are used in combination (the results from the models are included in the same report). The applicant advised the test results would not lead to a change of the main treatment option (i.e. RT), indicating results from the ASTuTE trial confirm this (person communication, applicant, 23 November 2024).

Figure 4 Clinical algorithm of initial therapy options for intermediate-risk prostate cancer according to NCCN guidelines



RP = radical prostatectomy, PLND = pelvic lymph node dissection, RT = radiotherapy, ADT = androgen deprivation therapy, ST-ADT = short-term androgen deprivation therapy.
Source: compiled by assessment group based on information in the NCCN clinical practice guidelines (NCCN 2024b)

Figure 5 Clinical management algorithms of current standard of care and intervention add-on



RT = radiotherapy, ADT = androgen deprivation therapy, ST-ADT = short-term androgen deprivation therapy, TURP = transurethral resection of the prostate, SoC = standard of care, DM = distant metastasis, NCCN = National Comprehensive Cancer Network, EAU = European Association of Urology.
Source: Compiled by the assessment group

Proposed economic evaluation

The application claimed that for patients with localised prostate cancer of intermediate risk planning to receive curative-intent RT, the ArteraAI Prostate Biopsy Assay is predictive of benefit from ST-ADT and is thereby superior in terms of health outcomes relative to current clinical practice (Application form, p.27 of the PICO Set). The main claim advanced in the application was that use of the ArteraAI Prostate Biopsy Assay for the proposed indication may reduce the use of ST-ADT in patients for whom treatment is likely to be futile, thereby avoiding the negative consequences of treatment and minimising unnecessary ST-ADT treatment costs in patients unlikely to benefit.

The application also claimed that, compared to the NCCN risk stratification tool, the ArteraAI Prostate Biopsy Assay models have superior discriminatory performance across distant metastasis (5- and 10-year), biochemical failure (5- and 10-year) and prostate cancer-specific survival outcomes, improving the value of knowing for patients (Application form, p.27 of the PICO Set).

The most appropriate economic evaluation is a cost-effectiveness or cost-utility analysis to determine costs relative to the test's effectiveness in improving patient-centred health outcomes (Table 9).

PASC noted the applicant's clinical claim that the ArteraAI assay is superior to the NCCN risk stratification tool for determining prognosis and leads to superior health outcomes for intermediate-risk patients when compared to current methods used to predict the benefit from ST-ADT. Therefore, PASC considered that the most appropriate economic evaluation for this application will be a cost-effectiveness or cost-utility analysis.

Table 9 Comparative effectiveness and safety of the proposed intervention and guide to the most suitable economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Noninferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	**CEA/CUA**

CEA = cost-effectiveness analysis, CMA = cost-minimisation analysis, CUA = cost-utility analysis

***Notes**: ? reflects uncertainties and any identified health trade-offs in the economic evaluation as a minimum in a cost–consequences analysis.*

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or comparative safety considerations.

[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence.

Proposal for public funding

The application proposed a new MBS item for the ArteraAI Prostate Biopsy Assay.

The ArteraAI Prostate Biopsy Assay is not yet listed on the ARTG (as of October 2024). A TGA application for this health technology is still in progress. According to the applicant (personal communication, 17

October 2024) the proposed population included in the TGA application includes (but is broader than) the population included in this proposal for public funding.

The draft MBS item descriptor proposed in the application (Application form, p.23 of the PICO Set) is shown in Table 10.

Table 10 Proposed MBS item descriptor in the application

Category 6 – PATHOLOGY SERVICES – P5 Tissue Pathology
MBS item XXXX ArteraAI Prostate Biopsy Assay for men with localised prostate cancer that have a National Comprehensive Cancer Network (NCCN) risk category of intermediate risk (favourable or unfavourable), who are planned to undergo curative-intent radiotherapy for prostate cancer, where intermediate risk is defined as follows: Has all of the following: ● No high-risk group features ● No very-high-risk group features ● Has one or more intermediate risk factors (IRFs): o Clinical stage cT2b-cT2c o Grade Group 2 or 3 (Gleason Score 7 [3+4] or Gleason Score 7 [4+3]) o PSA 10-20ng/mL Favourable intermediate risk: (has all of the following) • 1 intermediate risk factor (IRF) • Grade Group 1 or 2 (Gleason Score <6 or Gleason Score 7 [3+4]) • <50% biopsy cores positive (e.g., <6 of 12 cores) Unfavourable intermediate risk (has at least one of the following) • 2 or 3 IRFs • Grade Group 3 (Gleason Score 7) • ≥50% biopsy cores positive (e.g., >6 of 12 cores) The artificial intelligence prostate biopsy assay should not be used in patients with a diagnosis of metastatic cancer or those who have previously received cancer treatment of curative intent. The test may be used once per new prostate cancer diagnosis.
Fee: $1,200

Source: MBS item descriptor proposed in the application (Application form, p.23 of the PICO Set).

The proposed item descriptor was updated following discussion with the applicant and the department (personal communication, 17 October 2024). Amendments include:

- removal of gendered language
- removal of reference to other instruments (i.e. to the NCCN guidelines for defining intermediate risk in the eligible population)
- removal of the brand name of the test.

The updated item descriptor is shown in Table 11.

Table 11 Updated MBS item descriptor

Category 6 – PATHOLOGY SERVICES – P5 Tissue Pathology
MBS item XXXX Use of a software algorithm to return a prognosis and inform decisions regarding treatment with short-term androgen deprivation therapy for a patient where: (a) they have been diagnosed with localised non-metastatic histologically confirmed prostate cancer, and (b) their prostate cancer is considered to be of intermediate risk, and (c) they are planned to undergo curative-intent radiotherapy for their prostate cancer, and (d) they have not previously received cancer treatment of curative intent. No more than once per prostate cancer diagnosis
Fee: $1,200

Source: Draft MBS item descriptor as discussed during pre-PASC meeting. Red text indicates additional changes for consideration added after the pre-PASC meeting.

Table 12 presents the updated proposed MBS item incorporating PASC's advice.

Regarding the proposed item descriptor, PASC considered the following:

- *given the evidence presented relates to a specific algorithm, the descriptor should specify the trade name of the software algorithm*
- *intermediate risk should be defined*
- *frequency should be once per lifetime (in the context of this application [i.e. intermediate-risk patients planned for curative RT], PASC felt the frequency restriction would logically have to be once per lifetime, since the assay is unsuitable for patients who have previously undergone curative treatment)*
- *eligibility should be limited to a patient where a prostate cancer diagnosis is made on prostate core biopsy (given the AI algorithms were trained on core biopsy specimens)*
- *requesting should be restricted to specialists or consultant physicians.*

Table 12 Proposed MBS item descriptor (updated to incorporate PASC advice)

Category 6 – PATHOLOGY SERVICES – P5 Tissue Pathology
MBS item XXXX Use of ~~a software algorithm~~ *the ArteraAI Prostate Biopsy Assay* to return a prognosis and inform decisions regarding treatment with short-term androgen deprivation therapy for a patient where: (a) they have been diagnosed with localised non-metastatic histologically confirmed prostate cancer *(where the diagnosis is made on a prostate core biopsy)*; and *(b)* their prostate cancer is considered to be of intermediate risk, *defined by at least one of the following characteristics:* *(i) clinical stage T2b or T2c;* *(ii) grade group 2 or 3;* *(iii) prostate specific antigen level of 10 to 20ng/mL; and* (c) they are planned to undergo curative-intent radiotherapy for their prostate cancer; and (d) they have not previously received cancer treatment of curative intent. *Requested by a specialist or consultant physician* No more than once per ~~prostate cancer diagnosis~~ *lifetime*
Fee: $1,200

Note: Changes to the proposed item descriptor are presented in red text. Additions are shown in *italics* and deletions are in ~~strikethrough~~.

The application (p.22) noted that, in the context of future-proofing the MBS item descriptor, the criteria for intermediate risk may be omitted. In patients with localised prostate cancer of any risk group, the test may be used to provide more accurate risk stratification to inform shared decision-making regarding absolute benefit from various treatment approaches (Schaeffer et al. 2024). Nevertheless, the current request for public funding and the proposed item descriptor are restricted to use of the technology in patients with localised prostate cancer of intermediate risk planning to receive RT, where there is a clear treatment decision within which the tool may play a role (i.e. decision regarding the use of ST-ADT).

Proposed fee

The proposed fee suggested in the application was $1,200. This proposal will be confirmed during the assessment phase and determined on the basis of cost-effectiveness.

The initial proposed fee was informed by pricing of the test in the US (personal communication, applicant, 23 October 2024). The Center for Medicare and Medicaid Services 2024 lab fee schedule lists the ArteraAI Prostate Biopsy Assay (code 0376u) at USD706.25 (≈AUD1,045.27). The extended descriptor for item 0376u (Center for Medicare & Medicaid Services 2024) stipulates it is for the following:

> *'Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and PCSM, includes predictive algorithm to androgen deprivation-therapy response, if appropriate.'*

The applicant referenced existing MBS Pathology Services items for *BRCA1* or *BRAC2* testing (items 73295 and 73296) and EndoPredict (item 73306) to provide some context for the proposed fee in the Australian setting (personal communication, applicant, 23 October 2024). The fee for each of these 3 items is $1,200 (Table 13, Appendix). These items provide context only. The applicant informed that the proposed fee in the assessment report will be determined on the basis of cost-effectiveness (value-based pricing).

The proposed technology would be provided as an out-of-hospital procedure, therefore Medicare would fund 85% of the proposed item fee, with the patient paying the gap (Application form, p.23 of the PICO Set). Based on the proposed fee of $1,200, the gap exceeds the Greatest Permissible Gap (GPG) ($102.40 from 1 November 2024) as defined in Section 10(3) of the national *Health Insurance Act 1973* (Department of Health and Aged Care 2024b). Hence, the patient would pay the GPG and Medicare would pay the remainder.

The proposed MBS fee for the ArteraAI Prostate Biopsy Assay covers the cost to run the test and generate the report, plus the fee for the pathologist to check the image received to ensure the input variables from the test requisition form aligns with the image and to sign off on the test report (personal communication, applicant, 23 October 2024).

The ArteraAI Prostate Biopsy Assay currently accepts digital images from one of 2 scanners (Application From, p.12 of the PICO Set). Not all labs will have access to these scanners, meaning that in some instances, biopsy specimens would need to be transported to central labs for scanning and uploading for use by the proposed technology.

The cost of transporting samples between laboratories falls outside of the MBS item fee but this does not necessarily mean that the transport cost is not reimbursable or that there will be an out-of-pocket cost for sample transport (personal communication, Department of Health and Aged Care, 23 October 2024).

Patient episode initiation (PEI) items listed in Group 10 of the Pathology Services Category cover costs such as specimen collection, storage, transportation, reporting and the raising of accounts. Where a pathology provider refers a pathology service to another provider (e.g. if unable to undertake a certain service) the receiving pathology provider may be able to claim MBS item 73940 (Fee: $10.25) (personal communication, Department of Health and Aged Care, 23 October 2024).

Gerrard et al. (2024) showed the AI model generalised well from the research setting to the clinical setting (where a different scanner was used) but cautioned that this does not imply the AI models are scanner agnostic. Indeed, the authors suggest that, at this point, validation should be performed on a specific scanner before the AI is trusted to work on that model of scanner (Gerrard et al. 2024).

The applicant intends to expand the number of scanners that can be used with the proposed technology (personal communication, applicant, 17 October 2024).

PASC noted the proposed cost is informed by the cost of BCRA/EndoPredict in Australia and the cost of the intervention in the US. However, PASC considered it was inappropriate to benchmark the ArteraAI assay with EndoPredict as this utilises laboratory-based molecular genetic testing.

PASC noted the proposed fee is intended to cover the cost to run the test and generate the report. However, PASC noted that the laboratory performing the testing would likely be required to generate WSIs for other referral labs. Additionally, PASC noted no laboratory testing is involved (unlike other genetic assays) and considered this should be factored into the proposed price. Therefore, PASC requested the applicant to provide a detailed cost breakdown and justification for the proposed price in the assessment report.

PASC considered that the applicant should address what cost transfer arrangements would be in place between the pathology laboratories and Artera for the use of the ArteraAI assay, considering that the MBS fee would be paid to the pathology laboratory.

Other considerations

The application noted that a histopathologist needs to review and certify the results of the test. This includes checking the quality of the slides and digitised images, as well as checking that the input variables from the test requisition form and the image are aligned (personal communication, pre-PASC meeting, 17 October 2024). Histopathologists would be provided instructions on the ArteraAI tool, with support available as required. Clinical advice suggests that histopathologists are generally trained in the use of digitised WSIs and WSI scanners (personal communication, applicant, 17 October 2024).

A Digital Microscopy Education and Training Manual has been published by the RCPA (The Royal College of Pathologists of Australasia 2018). According to the RCPA website, part of the RCPA exam in anatomical pathology is digital microscopy based, and many educational programs and modules on the RCPA utilise WSIs (The Royal College of Pathologists of Australasia 2018). Requirements for use of digital images as an alternative to direct microscopy have also been published by the National Pathology Accreditation Advisory Council. These state the minimum best practice standards for the use of digital pathology (National Pathology Accreditation Advisory Council 2021).

The versions of the algorithms used clinically are 'locked' (do not continually learn as exposed to new information); however, there is scope for the algorithms used in the validation studies/assessed in this application to be updated in future. The applicant advises that quality assurance measures are in place to

ensure the algorithm does not become biased, specifically that model development follows the Good Machine Learning Practice for Medical Device Development: Guiding Principles identified by the Food and Drug Administration (FDA), Health Canada, and the Medicines and Healthcare Products Regulatory Agency (MHRA) (US Food & Drug Administration 2021).

The applicant advised that there is currently no process in place to use clinical patient information from Australian patients to further train the algorithm (personal communication, applicant, 17 October 2024). There is a practical consideration to this, as long-term clinical outcomes are needed to train the models and there are no current mechanisms to allow for this.

Subsequent therapies

The proposed item descriptor (Table 11) refers to the use of ST-ADT in patients with localised non-metastatic prostate cancer of intermediate risk. The application detailed that while several ADTs are listed on the PBS for use in patients with prostate cancer in Australia, treatment is restricted to locally advanced and/or metastatic disease (application form, p.8 of the PICO Set). A summary of the current PBS restrictions for ADT appears in the Appendix (Table 14).

Treatment of localised prostate cancer of intermediate risk also falls outside the conditions specified in the relevant ARTG listings (Therapeutic Goods Administration 2025). Nevertheless, a considerable number of patients with intermediate risk are treated with ADT off-label under current clinical practice. A prospective cohort study of men with intermediate- and high-risk prostate cancer who received definitive RT between January 2010 and December 2015 as part of the Prostate Cancer Outcome Registry Victoria showed that 32% (63/199) of men with favourable intermediate-risk disease and 46% (318/687) of men with unfavourable intermediate-risk disease who were treated with definitive RT received ADT (Ong et al. 2017). According to the Prostate Cancer Across Australia and New Zealand 2023 Annual Report, 16% of patients with intermediate-risk disease received RT and a further 9% received RT + ADT (i.e. approximately 36% of intermediate-risk patients treated with RT received it in conjunction with ADT) (Ong et al. 2024). Expert clinical advice confirms that use of ST-ADT in intermediate-risk disease is standard practice in the Australian setting (personal communication, applicant, 17 October 2024).

Summary of public consultation input

PASC noted and welcomed consultation input from 8 *organisations and 1 health professional. The 8 organisations that submitted input were:*

- Genitourinary Special Advisory Group of the Urological Society of Australia and New Zealand (USANZ)
- Prostate Cancer Foundation of Australia (PCFA)
- Genomics For Life
- TissuPath
- Urological Society of Australia and New Zealand (USANZ)
- GenesisCare
- Movember
- The Royal Australian and New Zealand College of Radiologists (RANZCR)

PASC noted no feedback was received from RCPA. PASC considered it was important to get input from RCPA Informatics and Anatomical Pathology Advisory groups.

The consultation input received ranged from supporting to not supporting public funding for ArteraAI Prostate Biopsy Assay for patients with localised prostate cancer, with USANZ and its Genitourinary Special Advisory Group and the RANZCR not supportive of public funding. The consultation input raised several concerns, predominately in relation to insufficient prospective evidence, lack of clinical need and the unlikelihood of the assay being cost effective.

PASC noted that key speciality societies (USANZ; RANZCR) were not currently supportive of this application. PASC noted that although USANZ was not currently supportive, this was based on its presumption of likely cost and cost-effectiveness; however, it did accept that evidence was available for the use of ArteraAI in patients with intermediate risk.

Consumer Input

The Movember Foundation and PCFA outlined the physical, social, cognitive and sexual side effects of ADT. Movember listed the specific adverse effects of ADT including decreased sexual function, bone density loss, weight gain, depression, hot flushes and vomiting. PCFA stated there is an unmet need for counselling and information on the side-effects of ADT to make an informed decision, in addition to the unmet need of supportive care.

Benefits and Disadvantages

The main benefits of public funding that were received in the consultation input included that the test is simple and provides greater clarity on who should receive ADT, and that overtreatment with ADT is reduced, thus avoiding the toxic side-effects of treatment.

The main disadvantages of public funding that were received in the consultation input included concerns that there is insufficient clinical evidence that AI predictive tools lead to a meaningful change in management; that it is unlikely to add value, as ADT use in the patient population is quite uncommon; and that funding would increase the cost with little or no benefit. The Genitourinary Special Advisory Group of USANZ stated that ArteraAI had the potential to add ADT to patients who would not currently be offered ADT, thereby increasing the overall use of ADT. Both RANZCR and Movember noted that ArteraAI has not yet undergone prospective clinical trials, an evidentiary requirement for other health interventions.

Population, Comparator (current management) and Delivery

The consultation input mostly agreed with the proposed population, noting that there are multiple risk stratification systems in use across Australia to identify patients with intermediate risk, with that of the National Comprehensive Cancer Network (NCCN) the most commonly used.

The consultation input agreed with the proposed comparator, with Movember stating it is not aware of any assay similar to ArteraAI available in Australia.

Other services identified during the consultation input as being needed to be delivered before or after the intervention, included the availability of approved scanners and laboratories for providing testing, training to implement the testing, education on report interpretation and counselling.

MBS Item Descriptor and Fee

Consultation input on the proposed item descriptor and fee was only provided by those who supported the application. All input agreed with the proposed item descriptor and fee, including Genomics For Life who provided the laboratory services of the clinical trial for the ArteraAI assay.

Additional Comments

RANZCR stated that an ethical governance framework is required for accountability for clinical decisions from the ArteraAI assay, and expressed concern that the software is trained on North American data that may not align with the Australian demographic.

Movember and PCFA both stated that the PBS restrictions should be reviewed prior to listing ArteraAI, as currently ADT is prescribed off-label in this population.

Next steps

PASC noted the applicant has elected to progress its application as an ADAR.

PASC noted that key specialty societies were currently not supportive of this application. Clinical support is a requirement for the application to progress. PASC suggested the applicant liaise with specialist societies to understand the reasoning for the lack of support and provide further information to the societies.

PASC noted that while the proposed fee is informed by the cost of BRCA*/EndoPredict, there is no genetic testing performed with the ArteraAI Prostate Biopsy Assay. PASC requested that the applicant to provide a more detailed cost justification in the assessment report, including a breakdown of cost components.*

PASC recognised that current clinical practice is not reflected in the ARTG listings or PBS restrictions for ADT. PASC raised concerns in asking MSAC to approve a test that may result in patients being prescribed a therapy outside the current PBS listings. PASC noted that this application was not progressing as a co-dependent application to both MSAC and PBAC. PASC recognised that the results of the ArteraAI test would be only one of several factors considered in a joint decision-making process as to whether or not to proceed treatment (RT) with additional ST-ADT, therefore true co-dependency is not present in this application. However, PASC considered that it would be appropriate for the issues raised regarding current clinical practice and the existing restrictions for ADT medicines on the PBS to be provided to PBAC Executive for its consideration of whether any further action would be appropriate.

The following questions raised by PASC/put forward to PASC remain unresolved:

- *Whether the Australian Department of Health and Aged Care has any framework in development around use and governance of AI in diagnostics/treatment planning? (PASC noted that the TGA is currently developing such a framework.)*
- *Who carries the responsibility (and medicolegal liability) for any error? (PASC noted that a pathologist is asked to sign-off on the test, but the test is unlike all other AI tools currently in use in anatomical pathology where AI is an aid, the results of which are checked by the pathologist. With ArteraAI, the pathologist cannot check that the logic is correct).*
- *Whether any secondary comparators are of relevance to this application? (Recent NCCN guideline updates identified 3 gene-panel tests as other advanced risk stratification tool options. The Decipher 22-gene panel, which has predictive features, may be particularly relevant; however, none*

of these tests are currently registered for use in Australia. A web-based clinical support tool [PREDICT Prostate] was also identified during scoping and is readily available; however, according to the applicant's clinical experts, it is not widely used in Australia.)

- *Whether there is sufficient prospective evidence available on the assay for the application to progress to ESC/MSAC (noting that the ASTuTE trial is underway in Australia)? (PASC noted that—following precedence set by prior MSAC considerations—in the absence or RCT evidence demonstrating predictive value, the application should provide evidence of an appropriate regulatory and quality assessment framework, an appropriate nomination of clinical place aligned with sufficiently robust clinical evidence of incremental prognostic value, an adequate justification of cost per test, and an acceptable total net financial cost to government.)*

Applicant Comments on Ratified PICO

The Applicant welcomes PASC's feedback and looks forward to progressing this Application to the ADAR stage.

The Applicant will liaise with relevant societies to ensure they are well informed in their decision whether to support the continued progress of the ArteraAI Prostate Biopsy Assay Application for the proposed patient population, or not. It is important to note that, as per the 2025 NCCN guidelines for prostate cancer (version 1), ArteraAI Prostate Test is recommended as a tool for informing prognosis and predicting benefit of ST-ADT (2A, Level 1B evidence).

Regarding the disconnect in current clinical practice and the PBS restrictions for ST-ADT, the Applicant notes that *"PASC considered that it would be appropriate for the issues raised regarding current clinical practice and the existing restrictions for ADT medicines on the PBS to be provided to PBAC Executive for its consideration of whether any further action would be appropriate".* The applicant notes that the main premise of the application is that current use outside the PBS restrictions for ST-ADT will be reduced.

Other issues mentioned and advice provided by PASC as per the Next Steps, are welcomed, and will be considered further during the ADAR process.

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Appendix

MBS listings of prior tests

Table 13: MBS items for PSA quantification, needle biopsies, relevant imaging investigations and prostate core biopsy histopathology

MBS Item	Description	Fee
37216	Prostate or prostatic bed, needle biopsy of, by the **transrectal route**, using prostatic **ultrasound** guidance and obtaining one or more prostatic specimens, being a service associated with a service to which item 55603 (ultrasound) applies	$160.00
37219	Prostate or prostatic bed, needle biopsy of, by the **transperineal route**, using prostatic **ultrasound** guidance and obtaining one or more prostatic specimens, being a service associated with a service to which item 55600 (ultrasound) or 55603 (ultrasound) applies	$384.05
37226	Prostate or prostatic bed, needle biopsy of, using prostatic **MRI** techniques and obtaining 1 or more prostatic specimens.	$320.00
63541	**Multiparametric MRI**—scan of the prostate for the **detection** of cancer, requested by a specialist in the speciality of urology, radiation oncology or medical oncology: (a) if the request for the scan identifies that the patient is suspected of developing prostate cancer: (i) on the basis of a digital rectal examination; or (ii) in the circumstances mentioned in clause 2.5.9A; and (b) using a standardised image acquisition protocol involving: (i) T2-weighted imaging; and (ii) diffusion-weighted imaging; and (iii) (unless contraindicated) dynamic contrast enhancement (R) Note: See explanatory note IN.5.1 for the meaning of Clause 2.5.9 in the descriptor for this item and the claiming limitations.	$492.65
66655	Prostate-specific antigen—quantitation For any particular patient, applicable not more than once in 23 months	$20.15
66659	Prostate-specific antigen (PSA), quantitation of 2 or more fractions of PSA and any derived index, including, if performed, a test described in item 66656, in the follow up of a PSA result under item 66654 or 66655 that lies at: (a) more than 2.0 ug/L but less than or equal to 5.5 ug/L for patients with a family history of prostate cancer; or (b) more than 3.0 ug/L but less than or equal to 5.5 ug/L for patients who are at least 50 years of age but under 70 years of age; or (c) more than 5.5 ug/L but less than or equal to 10.0 ug/L for patients who are at least 70 years of age For any particular patient, applicable not more than once in 11 months	$37.30
72823	Examination of complexity level 4 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions – 1 separately identified specimen	$97.15
72824	Examination of complexity level 4 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions – 2 to 4 separately identified specimens	$141.35
72825	Examination of complexity level 4 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions – 5 to 7 separately identified specimens	$180.25
72826	Examination of complexity level 4 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions – 8 to 11 separately identified specimens	$194.60

MBS Item	Description	Fee
72827	Examination of complexity level 4 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions – 12 to 17 separately identified specimens	$208.95
72828	Examination of complexity level 4 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions – 18 or more separately identified specimens	$223.30

MBS = Medicare Benefits Schedule, MRI = magnetic resonance imaging
Source: MBS (Department of Health and Aged Care 2024a)

MBS listings of other pathology services

Table 14 MBS listings of other pathology services

MBS item	Description	Fee
73295	Category 6 – Pathology Services, P7 – Genetics Detection of germline BRCA1 or BRCA2 pathogenic or likely pathogenic gene variants, requested by a specialist or consultant physician, to determine eligibility for treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor under the Pharmaceutical Benefits Scheme (PBS), in a patient with: (a) advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible; or (b) triple negative early breast cancer; or (c) hormone receptor positive, HER2-negative, early breast cancer with one or more high-risk characteristics. Applicable once per lifetime.	$1,200
73296	Category 6 – Pathology Services, P7 – Genetics Characterisation of germline gene variants, including copy number variation where appropriate, requested by a specialist or consultant physician: (a) in genes associated with breast, ovarian, fallopian tube or primary peritoneal cancer, which must include at least: (i) BRCA1 and BRCA 2 genes; and (j) one or more STK11, PTEN, CDH1, PALB2 and TP53 genes; and (b) in a patient: (i) with breast, ovarian, fallopian tube or primary peritoneal cancer; and (ii) for whom clinical and family history criteria place the patient at greater than 10% risk of having a pathogenic or likely pathogenic gene associated with breast, ovarian, fallopian tube or primary peritoneal cancer Once per cancer diagnosis	$1,200
73306	Category 6 – Pathology Services, P7 – Genetics Gene expression profiling testing using EndoPredict, for the purpose of profiling gene expression in formalin-fixed, paraffin-embedded primary breast cancer tissue from core needle biopsy or surgical tumour sample to estimate the risk of distant recurrence of breast cancer within 10 years, if: (a) the sample is from a new primary breast cancer, which is suitable for adjuvant chemotherapy; and (b) the sample has been determined to be oestrogen receptor positive and HER2 negative by IHC and ISH respectively on surgically removed tumour; and (c) the sample is axillary node negative or positive (up to 3 nodes) with a tumour size of at least 1 cm and no more than 5 cm determined by histopathology on surgically removed tumour; and (d) the sample has no evidence of distal metastasis; and (e) pre-testing of intermediate risk of distant metastases has shown that the tumour is defined by at least one of the following characteristics: (i) histopathological grade 2 or 3; (ii) one to 3 lymph nodes involved in metastatic disease (including micrometastases but not isolated tumour cells); and (f) the service is not administered for the purpose of altering treatment decisions Applicable once per new primary breast cancer diagnosis for any particular patient	$1,200

Source: Compiled by assessment group based on information provided by the applicant (personal communication, 23 October 2024) and available on the MBS (Department of Health and Aged Care 2024a)

PBS listings for androgen deprivation therapy

Table 15 PBS listings for androgen deprivation therapy

Drug	Code	PBS restriction	Inclusive of proposed population
LH-RH agonists			
Goserelin	8093Y 1454M	Locally advanced (stage C) or metastatic (stage D) carcinoma of the prostate	No
Leuprorelin	11943N 8708H 8876E 8709J 8877F 8859G 8875D 8707G		
Triptorelin	9379P 9378N 5297T		
LH-RH antagonists			
Degarelix	2784M 2785N	Locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate	No
Antiandrogens			
Bicalutamide	8094B	Metastatic (stage D) carcinoma of the prostate Treatment must be in combination with GnRH (LH-RH) analogue therapy	No
Flutamide	1417N		
LH-RH agonist plus antiandrogen			
Goserelin and bicalutamide	9065D 9064C 9066E	Metastatic (stage D) carcinoma of the prostate Patient must require a combination of an antiandrogen and a GnRH (LH-RH) agonist	No
Leuprorelin and bicalutamide	10962Y 10969H 10963B		
CYP17 inhibitors			
Abiraterone	11206T 2698B	Castration-resistant metastatic carcinoma of the prostate Must be used in combination with a corticosteroid and chemotherapy	No
Abiraterone & Methylprednisolone	14078Y 13263C	Metastatic castration-sensitive carcinoma of the prostate Must be used in combination with chemotherapy	No

GnRH = gonadotropin-releasing hormone, LH-RH = luteinising hormone–releasing hormone agonist, PBS = Pharmaceutical Benefits Scheme
Source: Compiled by assessment group based on information provided in the application (pp 7–8) and available on the PBS (Department of Health and Aged Care 2024c).