MSAC Application 1816

Genetic testing to detect estrogen receptor 1 (*ESR1*) variants in patients with hormone receptor (HR)-positive, HER-2 negative, locally advanced or metastatic breast cancer to determine eligibility for treatment with PBS subsidised camizestrant

Applicant: AstraZeneca Pty Ltd

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 genetic testing to detect estrogen receptor 1 (*ESR1*) variants in patients with hormone receptor (HR)-positive, HER-2 negative, locally advanced or metastatic breast cancer to determine eligibility for treatment with PBS subsidised camizestrant.

Component	Description
Population	**Test:** Patients with ER+/HER2- locally advanced or metastatic breast cancer who have received first line treatment with a CDK4/6 inhibitor in combination with an aromatase inhibitor (AI) for at least 6 months, and whose disease has not progressed clinically or radiographically. **Treatment:** Those patients above that test positive for an *ESR1* variant.
Prior tests	Tests required to confirm diagnosis of breast cancer (i.e. biopsy and histopathology) Tests required to confirm stage of cancer (i.e. mammogram or ultrasound, lymph node assessment, computed tomography, magnetic resonance imaging) Tests required to confirm biomarker status (immunohistochemical evaluation for HR+/HER2-)
Intervention	**Test:** Genetic testing to detect *ESR1* variants in circulating tumour DNA (ctDNA) extracted from blood (liquid biopsy). **Treatment:** Camizestrant in combination with CDK4/6 inhibitor (ribociclib, palbociclib, abemaciclib) for patients found to have an *ESR1* variant.
Comparator/s	**Test comparator:** No testing for *ESR1* variants. **Treatment comparator:** Continued standard of care (SOC) first line therapy (CDK4/6 inhibitor [ribociclib, palbociclib, abemaciclib] in combination with an AI [anastrozole, letrozole, exemestane]).
Reference standard	There is no reference standard for genetic testing. In the absence of a reference standard, concordance between *ESR1* variants testing assays could be utilised (NGS vs ddPCR).
Clinical utility standard	In the key clinical trial, SERENA-6, the Guardant360® CDx test was used to identify *ESR1* variants in ctDNA extracted from blood (liquid biopsy) through NGS. Testing was undertaken every 2-3 cycles (8-12 weeks), coinciding with routine clinical visits conducted in concordance with patient management guidelines for HR+/HER2- advanced breast cancer.

Outcomes	**Test Outcomes** *Efficacy/ Effectiveness* • Diagnostic accuracy (sensitivity, specificity, PPV, NPV), test-retest reliability *Other test-related considerations* • Number needed to test (to identify one eligible case for treatment) • Test turn-around time • Rate of re-testing (including test failure) *Comparative performance of* ESR1 *variant testing methods* • Concordance between *ESR1* variant testing assays (NGS vs ddPCR) • Re-testing rate • Concordance between Guardant360 CDX/VHIO360 vs Australian NGS assays (Oncomine™ Precision Assay and Pillar Biosciences OncoReveal® Essential LBx) *Clinical utility of the test* • Percentage of patients changing treatment plan *Safety* • Adverse outcomes related to testing. **Treatment outcomes** *Efficacy/effectiveness* • Progression-free survival (PFS) • Overall survival (OS) • Overall response rate (ORR), complete response (CR), partial response (PR), stable disease (SD) • Health-related quality of life (HRQoL) *Safety* • Treatment-emergent adverse events **Healthcare resources** • Costs of delivering the testing intervention including ongoing monitoring • Costs of delivering the treatment (including cost of treatment for additional or incidental findings) • Costs of managing adverse events • Cost-effectiveness of test and treatment • Financial implications of test and treatment

Component	Description
	Total Australian government healthcare costs • Total cost to the Medicare Benefits Schedule (MBS) for testing • Total cost to the Pharmaceutical Benefits Scheme (PBS) for treatment • Total cost to other healthcare services
Assessment questions	What is the safety, effectiveness and cost-effectiveness of genetic testing for *ESR1* variants and subsequent camizestrant treatment (in combination with a CDK4/6 inhibitor) versus no testing for *ESR1* variants and continued SOC first line treatment (CDK4/6 inhibitor in combination with an AI) in patients with HR+/HER2- locally advanced or metastatic breast cancer who have received at least 6 months of treatment with a CDK4/6 inhibitor in combination with an AI and whose disease has not yet progressed clinically or radiographically.

Purpose of application

The codependent application requested:

- Medicare Benefits Schedule (MBS) listing of genetic testing to detect estrogen receptor 1 (*ESR1*) variants in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-), locally advanced or metastatic breast cancer who have received first line treatment with a CDK4/6 inhibitor in combination with an aromatase inhibitor (AI) for at least 6 months, and whose disease has not progressed clinically or radiographically, to determine PBS eligibility for camizestrant treatment (in combination with a CDK4/6 inhibitor); and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of camizestrant for the treatment of HR+/HER2- locally advanced or metastatic breast cancer in patients who have received 1L treatment with a CDK4/6 inhibitor in combination with an AI for at least 6 months, and whose disease has not progressed clinically or radiographically and who test positive for an *ESR1* variant.

The applicant claims that genetic testing to identify *ESR1* variants, combined with targeted therapy with camizestrant (in combination with a CDK4/6 inhibitor), results in superior health outcomes compared to no testing and standard of care (SOC) first line treatment in patients with HR+/HER2- locally advanced or metastatic breast cancer, who have received first line treatment with a CDK4/6 inhibitor in combination with an AI for at least 6 months, and whose disease has not progressed clinically or radiographically.

PICO criteria

Population

The proposed testing population comprises patients with newly diagnosed HR+/HER2- locally advanced or metastatic breast cancer, who have received first line treatment with a CDK4/6 inhibitor in combination with an AI for at least 6 months, and whose disease has not progressed clinically or radiographically. The proposed treatment population is those patients above who test positive for an *ESR1* variant.

Background

In Australia, breast cancer is the second most diagnosed cancer (most common in women) and the fifth most common cause of cancer death (second most common in women), with an estimated 20,336 new cases diagnosed and 3,353 deaths in 2025 (Cancer Australia 2025).

Due to funded breast screening programs and education on self-examination, approximately 80% of breast cancers are diagnosed in Stages I-II (contained in the breast or spread to axillary lymph nodes only) (AIHW 2025). Early diagnosis results in a more favourable prognosis, with reported 5-year survival rates of 100% (stage I) and 94.6% (stage II) respectively (Cancer Australia 2019). Patients diagnosed in the advanced stages of the disease, when the tumour has spread significantly within the breast (locally advanced [Stage III]) or to other organs in the body (metastatic [stage IV]), have lower 5-year survival rates (80.6% for Stage III, dropping dramatically to 32% for Stage IV) (Cancer Australia 2019). Approximately 30% of patients initially diagnosed with early stage disease will subsequently develop advanced disease in the months or years after (Redig and McAllister 2013).

Advanced breast cancer is considered incurable, with the main goals of therapy being to delay disease progression and prolong survival, while minimising treatment toxicity and preserving health-related quality of life (HRQoL) (Harbeck et al. 2019).

Management

The European Society for Medical Oncology (ESMO) clinical guidelines recommend that patients with newly diagnosed or recurrent metastatic breast cancer should have a tissue biopsy to confirm histology and assess prognostic biomarkers to inform treatment options (namely estrogen receptor [ER], progesterone receptor [PR] and human epidermal growth factor receptor 2 [HER2]) (Gennari et al. 2021). Tumours expressing ER and/or PR are categorised as hormone receptor-positive breast cancers (HR+), whilst tumours that do not express ER, PR or HER2 are categorised as triple-negative breast cancer (Harbeck et al. 2019). The most common molecular subtype is HR+/HER2- which accounts for ~70% of cases of breast cancer (National Cancer Institute 2025).

Other therapeutically relevant biomarkers recommended to be assessed as part of routine clinical practice in patients with HR+/HER2- metastatic breast cancer include germline *BRCA1/2* and *PIK3CA* variant status (Gennari et al. 2021). Genomic profiling and further diagnostic tests [e.g. on tumour tissue or circulating tumour DNA (ctDNA)] are recommended to only be carried out as part of routine clinical practice if the result will change the treatment approach or if the patient can access appropriate clinical trials (Gennari et al. 2021).

The proposed diagnostic work-up algorithm for newly diagnosed or recurrent metastatic breast cancer from the ESMO guidelines is presented in Figure 1.

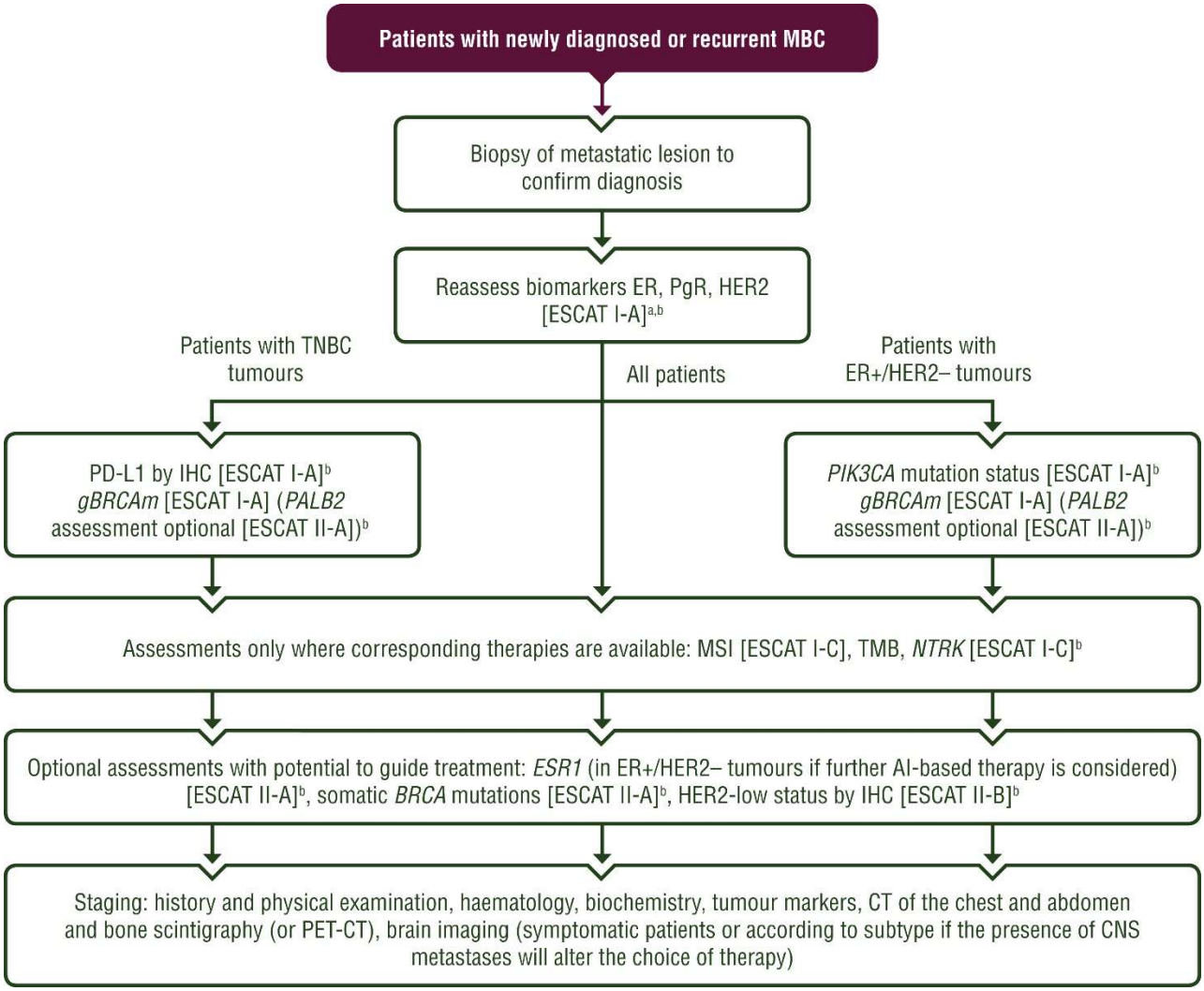

Figure 1 Diagnostic work-up and staging of metastatic breast cancer

AI = aromatase inhibitor; CNS = central nervous system; CT = computed tomography; ER = estrogen receptor; ESCAT = ESMO Scale for Clinical Actionability of Molecular Targets; *ESR1* = estrogen receptor 1; *gBRCAm* = germline *BRCA1/2* mutation; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; MBC = metastatic breast cancer; MSI = microsatellite instability; *NTRK* = neurotrophic tyrosine receptor kinase; *PALB2* = partner and localiser of *BRCA2*; PD-L1 = programmed death-ligand 1; PET = positron emission tomography; PgR = progesterone receptor; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TMB = tumour mutation burden; TNBC = triple-negative breast cancer.

Source: Figure 1, (Gennari et al., 2021)

Except for patients with visceral crisis (imminent organ failure) in whom chemotherapy is recommended, endocrine therapy, with either aromatase inhibitors (AIs) or fulvestrant, plus a CDK4/6 inhibitor is the recommended SOC first-line treatment for patients with HR+/HER2- locally advanced or metastatic breast cancer (Gennari et al. 2021). However, all tumours will eventually develop resistance to endocrine therapies, with *ESR1* variants representing a type of acquired resistance in up to 40-50% of patients after initial endocrine therapy in the metastatic setting (Brett et al. 2021).

There is no optimal sequence of therapy following disease progression after first-line treatment; it is dependent on disease aggressiveness, organ function, biomarkers, which agents were used previously and consideration of associated toxicities (Gennari et al. 2021). In general, sequential endocrine therapy is recommended unless there is imminent organ failure (where chemotherapy is recommended), until all endocrine therapy options have been exhausted or where there is evidence of endocrine resistance

(Gennari et al. 2021). However, clinical benefits from subsequent treatments are limited and diminish with each line of therapy, with poorer treatment responses associated with patients who acquire *ESR1* variants (Turner et al. 2020).

Endocrine resistance from acquired *ESR1* variants

However, all tumours will eventually develop resistance to endocrine therapies, with *ESR1* variants representing a type of acquired resistance in up to 40-50% of patients after initial endocrine therapy in the metastatic setting (Brett et al. 2021). *ESR1* variants alter the conformation of the ER ligand binding domain that results in ligand independent ER activation and constitutive ER signalling that promotes tumour growth and resistance (Brett et al. 2021). They are rarely detected prior to treatment initiation (estimated to be less than 5%) (Popović et al. 2025), occurring more frequently with longer exposure to endocrine therapy (Brett et al. 2021). Evidence suggests that detection of *ESR1* variants is associated with poor treatment outcomes in terms of progression-free survival (PFS) and overall survival (OS) (Turner et al. 2020), mainly owing to a lack of effective treatment options. Once patients progress on first line therapy, subsequent endocrine based therapies have limited efficacy, and patients will eventually require treatment with chemotherapy.

However, the availability of highly sensitive circulating tumour DNA (ctDNA) technology allows early detection of *ESR1* variants before radiologic or clinical disease progression has occurred. Switching from endocrine therapy to camizestrant at this early stage, ahead of disease progression, to target *ESR1* variants has the potential to extend PFS and maintain health-related quality of life (HRQoL) (Bidard et al. 2025).

Camizestrant therapy

Camizestrant is an oral next generation selective oestrogen receptor downgrader (SERD) and complete ER antagonist. Camizestrant binds to the ligand binding domain of the Estrogen receptor alpha (ERα) receptor, antagonising the activity of both wild-type ERα and those encoded by *ESR1* variants, and inducing proteasome-dependent degradation without agonising ERα (Bidard et al. 2025).

An early switch of the endocrine therapy backbone from AI to camizestrant in patients on first line treatment with a CDK4/6 inhibitor, upon emergence of *ESR1* variants, has been shown in the phase 3 randomised controlled trial, SERENA-6, to prolong the PFS benefit of first line therapy (Bidard et al. 2025). This approach effectively delays the resistance to treatment that ultimately leads to clinical disease progression and decline in HRQoL (Bidard et al. 2025).

The trial population in SERENA-6 included adult patients with ER+/HER2- locally advanced or metastatic breast cancer who had received at least 6 months of treatment with an AI plus a CDK4/6 inhibitor and had no evidence of disease progression.

PASC noted the proposed test population is "patients with newly diagnosed HR+/HER2- locally advanced or metastatic breast cancer, who have received first line treatment with a CDK4/6 inhibitor in combination with an AI for at least 6 months, and whose disease has not progressed clinically or radiographically"

PASC noted that:

- *The application is based on results from the SERENA-6 trial, which recruited ER-positive patients only*

- *The broader HR-positive population (proposed in the application) would include patients who are ER-negative, PR-positive*
- *The clinical utility of testing the ER-negative group is unclear, given camizestrant is a selective estrogen receptor downregulator (SERD)*

As such, the PASC proposed that the population should specify "Patients with ER+/HER2- locally advanced or metastatic breast cancer" to align with the main evidence base and exclude the ER-negative population.

Estimates for size of the testing population

For investigative technologies, the incidence and prevalence of the target population for the test is required; no estimates were provided by the applicant.

As per the study design of SERENA-6, some patients will require more than one *ESR1* variant test, as *ESR1* variants develop over time i.e. the requested MBS listing is for serial testing in patients who have HR-positive, HER2-negative locally advanced or metastatic breast cancer and have received at least 6 months of first line treatment with a CDK4/6 inhibitor plus an AI and who have not progressed radiographically or clinically. The applicant proposed that testing could be conducted every 2-3 months (from 6 months after initiation of first line therapy), to coincide with routine clinical assessments. Commencement of testing from 6 months was chosen to align with the proposed test population based on eligibility criteria from the SERENA-6 trial (which required patients to have received at least 6 months of first line therapy with a CDK4/6i plus an AI) (Bidard et al. 2025).

In SERENA-6, the median time from initiation of therapy with an AI plus a CDK4/6 inhibitor to detection of *ESR1* variant was 21 months (range 5-96 months); approximately 63% of patients had ≥ 18 months of first line treatment before *ESR1* detection (Bidard et al. 2025). The Palbociclib and ctDNA for *ESR1* variant detection (PADA-1) trial revealed that in patients receiving 1L therapy with an AI plus a CDK4/6i for advanced breast cancer, *ESR1* variants were detected in ctDNA at a median of approximately 6 months before disease progression (Bidard et al. 2022). An examination of median PFS reported in clinical trials of PBS-listed CDK4/6 inhibitors (in combination with an AI) for first line treatment of HR+/HER2- locally advanced or metastatic breast cancer ranged from 24.8 months to 28.2 months (see Table 2).

Table 2 PFS benefits of first line treatment with PBS listed CDK4/6 inhibitors in combination with an AI

PBAC PSD	Population	Trial ID	Treatment regimen/ median PFS (95% CI)	Comparator/ median PFS (95% CI)	Difference in median PFS
Abemaciclib - March 2019	Non-premenopausal patients with HR+/HER2- advanced breast cancer	MONARCH-3	Abemaciclib plus anastrozole or letrozole) 28.2 months (23.5, NR)	Placebo plus anastrozole or letrozole) 14.8 months (11.2, 19.2)	13.4 months
Palbociclib – March 2017, November 2017, March 2018	Non-premenopausal patients with HR+/HER2- advanced breast cancer	PALOMA-1 PALOMA-2	Palbociclib plus letrozole 24.8 months (22.1, NR)	Letrozole only 14.5 months (12.9,17.1)	10.3 months
Ribociclib – July 2017, November 2017, March 2018	Non-premenopausal patients with HR+/HER2- advanced breast cancer	MONALEESA-2	Ribociclib plus letrozole 25.3 months (23.0,30.3)	Letrozole only 16.0 months (13.4,18.2)	9.3 months

AI = aromatase inhibitor; CDK4/6 = cyclin dependent kinase 4/6; CI = confidence interval; HER2 = human epidermal growth factor 2; HR = hormone receptor; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression-free survival; PSD = Public Summary Document

PASC noted no estimates for the size of the patient population or testing population were provided in the pre-PASC PICO however acknowledged that estimates will be presented by the applicant in the integrated codependent submission to PBAC and MSAC.

PASC noted that most patients (83.2%) in the SERENA-6 trial were tested repeatedly every 2-3 months during the surveillance period without detecting an ESR1 *positive result. PASC considered that this would represent a substantial cumulative cost. PASC noted that most patients (60%) in the SERENA-6 trial were still in ongoing surveillance when screening closed [n=1949], i.e. remaining patients in the trial demonstrated no disease progression and were not* ESR1 *positive. PASC queried how long the surveillance period was in SERENA-6 (this information could not be found in the published paper) and what proportion of patients had disease progression during the surveillance period without testing* ESR1 *positive.*

Intervention

Test

The proposed medical service is genetic testing to identify *ESR1* variants in circulating tumour DNA (ctDNA) extracted from blood (liquid biopsy) in patients with HR+/HER2- locally advanced or metastatic breast cancer who have received first line treatment with a CDK4/6 inhibitor in combination with an AI for at least 6 months, and whose disease has not progressed clinically or radiographically, to determine eligibility for PBS-subsidised camizestrant in combination with the same CDK4/6 inhibitor they are already receiving (predictive test).

This is consistent with the key clinical trial, SERENA-6, where patients (who had received at least 6 months of first line therapy with a CDK4/6i plus an AI) were tested for *ESR1* variants in ctDNA extracted from blood (liquid biopsy) every 2-3 months (coinciding with routine clinical assessments), whilst remaining free of

disease progression (Bidard et al. 2025). However, although the enrolment criteria for the trial was that patients had to have received at least 6 months of the stated first line therapy, the median time from initiation of therapy with an AI plus a CDK4/6 inhibitor to detection of *ESR1* variant was 21 months (range 5-96 months); approximately 63% of patients had ≥ 18 months of first line treatment before *ESR1* detection (Bidard et al. 2025). This meant that in practice a majority of patients had been on first line therapy for much longer than 6 months which may explain why a slight majority (approximately 54%) had ESR1 detected on their first test. The applicant states that further details on the number of tests administered in the trial and what is expected to happen in practice will be presented in the integrated co-dependent submission.

NCCN, ESMO and ASCO clinical guidelines recommend testing for *ESR1* variants in ctDNA extracted from blood (liquid biopsy) as opposed to tissue biopsy (including archived tissue) (Burstein et al. 2023; Gennari et al. 2021; NCCN 2023), owing to greater sensitivity for identifying *ESR1* variants (Turner et al. 2020) and ease of use (repeated tests may be required, and multiple tissue biopsies are not practical and inconvenient for a patient).

ESR1 variants can be identified in liquid biopsy through next-generation sequencing (NGS) or digital droplet PCR (ddPCR) techniques. NGS can be used to detect multiple genetic changes (including rare or unknown variants), while ddPCR is used to detect known variants and only a few variants can be probed at one time (Davidson et al. 2021). It should also be noted that activating *ESR1* variants occur in hotspot regions, enabling efficient targeted testing. In the SERENA-6 clinical trial, the Guardant360® CDx test (Guardant Health 2025) was used, which assessed *ESR1* variants using a NGS method.

ESR1 variant testing would be requested by the treating clinician (most likely a medical oncologist) who would order the test at the same time as other routine blood monitoring (every 2-3 months).The sample will be sent to a clinical laboratory where a registered molecular pathologist and/ or a registered anatomical pathologist are responsible for conducting the detection, diagnosis and reporting of the pathology results which guide and determine treatment.

Medicare benefits are only eligible for pathology services rendered by an Australian accredited pathology laboratory. The pathologist providing the service must be an Approved Pathology Practitioner (APP) with a Medicare provider number that is linked to an Accredited Pathology Laboratory (APL) owned by an Approved Pathology Authority (APA). Pathology laboratories performing testing would need to be NATA-accredited, and as per other cancer biomarker genomic tests, competence in *ESR1* variant testing would be monitored via an appropriate Quality Assurance Program (QAP) such as one by the Royal College of Pathologists of Australasia (RCPA).

Special training (education and awareness) from the pathology laboratories may be required at collection centres to ensure that blood samples are collected and transported in special tubes that are suitable for sample stability and for subsequent ctDNA testing.

MSAC previously noted that when considering application 1782 (genetic testing for *ESR1* variants in ctDNA to determine eligibility for treatment with elacestrant) in April 2025 that there were no laboratories that are NATA accredited to undertake *ESR1* testing. At the pre-PASC meeting, the applicant stated that each state has a laboratory that is capable of ctDNA testing, however, not every state has a laboratory which is validated for liquid biopsy.

Treatment

Following genetic testing for *ESR1* variants using ctDNA from liquid biopsy:

- Patients who have identified *ESR1* variants would be eligible to receive camizestrant treatment in combination with the same CDK4/6 inhibitor they are already receiving
- Patients without identified *ESR1* variants would continue to receive the same CDK4/6 inhibitor in combination with an AI they are already receiving

The SERENA-6 trial demonstrated the clinical utility of testing ctDNA for *ESR1* variants and switching from AI to camizestrant in this patient population, with patients who switched to camizestrant having a significantly longer PFS period of almost 7 months (HR 0.44 95% CI 0.31-0.60, p<0.0001), while experiencing a reduced risk of deterioration in patient reported overall health and QoL, compared to those who maintained the AI combination treatment (Bidard et al. 2025).

As per the proposed treatment population for camizestrant, eligible patients must not have disease progression on 1L therapy (either clinically or radiographically). In SERENA-6, tumour assessments were performed by means of CT or MRI imaging at screening (within 4 weeks before randomisations), every 8 weeks for the first 18 months and then every 12 weeks until disease progression had occurred (Bidard et al. 2025). In Australia, there is currently a gap in the MBS for imaging of patients to adopt this monitoring approach; there are items for PET scans (MBS items 61525 for evaluation of suspected metastatic or locally/regionally recurrent breast cancer for patient considered suitable for active therapy), mammography (MBS items 59300/59303 for mammography of both/one breast/s if there is reason to suspect the presence of malignancy because of (i) past occurrence of breast malignancy in the patient, or (iii) symptoms or indications of breast disease found on examination by a medical practitioner) but not CT scans. For MRI scans, MBS item 63464 specifies a "MRI scan of both breast for the detection of cancer in a patient if ….. (b) the request for the scan identifies that the patient is asymptomatic and is younger than 60 years of age; and ….applicable not more than once in a 12 month period" , while MBS item 63647 is for "MRI-scan of both breast for the detection of cancer, if… (b) the person has had an abnormality detected as a result of a service mentioned in item 63464 in the previous 12 months". So, while there is a possibility of an MBS-funded MRI scan every 12 months for a subgroup of patients, overall there is a lack of MBS-funded imaging services to align with the monitoring approach adopted in the SERENA-6 trial.

PASC considered that no changes were required to the proposed test/treatment interventions.

PASC noted that camizestrant targets breast cancers that are ER positive and can either have a ESR1 variant present or are wild-type. Therefore, PASC queried whether camizestrant could be used upfront without ESR1 *testing. PASC noted that the on-going phase III trial SERENA-4 is investigating this scenario by comparing camizestrant + CDK4/6i vs AI + CDK4/6i in patients with ER+/HER2- locally advanced or metastatic breast cancer (Primary completion date August 2026). PASC queried when the interim analysis/PFS data will be available and how the results of the SERENA-4 trial may affect this application. PASC noted the applicant's comments that the results from the SERENA-4 trial will be available REDACTED, and they will provide more information about how the trial will affect this application once they have analysed those results.*

The PASC noted that, as per the SERENA-6 design, the applicant proposed testing every 2-3 months from at least 6 months after commencement of 1L therapy for patients who had not experienced disease

progression; testing would continue until an ESR1 *variant was detected or until disease progression. However, in the SERENA-6 trial the median time to* ESR1 *detection from commencement of 1L therapy was 21 months (range 5-96 months). As such, PASC recommended that the integrated codependent submission present sensitivity analyses to compare the yield and cost of testing when starting testing at 6, 12 or 18 months after commencement of 1L therapy. PASC noted that MSAC previously supported testing once every 3 months for application 1782.*

PASC noted that the Royal College of Pathologists Australia Quality Assurance program (RCPAQAP) are partnered with the European Molecular Quality Network (EMQN) for the provision of their External Quality Assessments (EQA) in Australia. PASC noted that the EMQN started an EQA scheme in 2024 for breast cancer ESR1 *testing in plasma and expect EQA accreditation in 2027.*

Comparator(s)

Test

The nominated comparator is no test.

Currently, there are no MBS listed tests available to identify patients with *ESR1* variants.

Treatment

The comparator is continued SOC first line treatment for patients with HR+/HER2- locally advanced or metastatic breast cancer (CDK4/6 inhibitor in combination with an AI).

Current PBS listed CDK4/6 inhibitors include ribociclib, palbociclib, abemaciclib, while current PBS listed AIs include anastrozole, letrozole and exemestane.

Fulvestrant is an alternative first line endocrine therapy option for HR+/HER2- locally advanced or metastatic breast cancer that can be delivered as a monotherapy or in combination with a CDK4/6 inhibitor and is PBS listed for this indication. Additionally, chemotherapy is a treatment option for patients with visceral crisis (imminent organ failure).

The PASC agreed with the test and treatment comparators proposed in the draft PICO confirmation.

Reference standard (for investigative technologies only)

There is currently no reference standard for genetic testing. Detection assays for *ESR1* variants in ctDNA include NGS and ddPCR, with ddPCR the most sensitive (Liao et al. 2020). The applicant claimed that concordance studies between these testing methodologies are currently underway and will determine which methodology is recommended in the integrated co-dependent submission.

PASC noted that ESR1 *variant detection in ctDNA can be conducted using either NGS or digital PCR (dPCR) and that the applicant advised that both are available in Australian laboratories.*

PASC noted that only NGS was used for ESR1 *testing in the SERENA-6 trial; as such information on how dPCR compares with NGS for* ESR1 *testing is required. PASC noted that MSAC cited two meta-analyses comparing these methodologies in the PSD for application 1782 which found:*

- *No significant difference in* ESR1 *variant incidence between ddPCR and NGS in both ctDNA extracted from blood (liquid biopsy) or tissue biopsy (Najim et al. 2023).*
- *Specificity of NGS (90.1%) and digital PCR (90.4%) was comparable, but sensitivity for NGS (56.8%) was lower than for digital PCR (81.0%) in detecting* ESR1 *variants in ctDNA extracted from blood (liquid biopsy) (Raei et al., 2024).*

Clinical utility standard (for codependent investigative technologies only)

In the SERENA-6 clinical trial, *ESR1* variant status was evaluated in ctDNA extracted from blood (liquid biopsy) using the Guardant360® CDx test (Bidard et al. 2025). The Guardant360® CDx uses NGS and high throughput hybridisation-based capture technology to detect single nucleotide variants (SNVs), insertions and deletions (indels), copy number amplifications (CNAs) and fusions in a targeted panel of 55 genes (Guardant Health 2025).

The applicant stated that the Guardant360® CDx is not available in Australia and that they are exploring the use of NGS within existing laboratories in Australia for the purposes of this MBS item. At the pre-PASC meeting the applicant stated they are currently conducting concordance studies between Australian assays using NGS to detect *ESR1* variants and Guardant360® CDx.

PASC noted that the Guardant360 CDx NGS test was used to detect ESR1 variants in the key clinical trial SERENA-6 (this test is the clinical utility standard). However, PASC noted that this specific NGS test is not available in Australia.

PASC noted the applicant is conducting a study to provide critical evidence for the analytical performance and concordance between two NGS assays (REDACTED and REDACTED), both available in Australia) and REDACTED (European based ctDNA panel using Guardant360 technology) for the detection of ESR1 variants in ctDNA, with a full comparison to be presented in the integrated PBAC/MSAC submission.

PASC noted that Peter MacCallum Cancer Centre (PMCC) has received NATA accreditation for ESR1 testing using the Oncomine Precision Assay and that LifeStrands also offers ctDNA ESR1 *NGS testing.*

Outcomes

The SERENA-6 trial provides direct evidence of the clinical utility of using *ESR1* variant status as a predictive biomarker for the benefits of treatment with camizestrant in patients with HR+/HER2- locally advanced or metastatic breast cancer who have received first line treatment with a CDK4/6 inhibitor in combination with an AI for at least 6 months, and whose disease has not progressed clinically or radiographically following at least one line of endocrine therapy, including a CDK4/6 inhibitor.

The following outcomes are relevant for MSAC decision making:

<u>Test outcomes</u>

Efficacy/effectiveness

- Diagnostic accuracy (Sensitivity, Specificity, PPV, NPV), test-retest reliability

Other test-related considerations

- Number needed to test (to identify one eligible case for treatment)
- Test turn-around time
- Rate of re-testing (including test failure)

Comparative performance of ESR1 *variant testing methods*

- Concordance between *ESR1* variant testing assays (NGS vs ddPCR)
- Re-testing rate
- Concordance between Guardant360 CDX/REDACTED vs Australian NGS assays (REDACTED and REDACTED)

Clinical utility of the test

- Percentage of patients changing treatment plan

Safety outcomes

- Adverse events related to testing

Treatment outcomes

Efficacy/effectiveness

- Progression-free survival (PFS)
- Overall survival (OS)
- Objective response (complete response or partial response)
- Health-related quality of life (HRQoL)

Safety Outcomes

- Treatment-emergent adverse events

Healthcare resources

- Costs of delivering the testing intervention including ongoing monitoring
- Costs of delivering the treatment (including cost of treatment for additional or incidental findings)
- Costs of managing adverse events
- Cost-effectiveness of test and treatment
- Financial implications of test and treatment

Total Australian government healthcare costs

- Total cost to the Medicare Benefits Schedule (MBS) for testing
- Total cost to the Pharmaceutical Benefits Scheme (PBS) for treatment
- Total cost to other healthcare services

The SERENA-6 trial had both a surveillance period for *ESR1* variants (eligible patients were tested for *ESR1* variants once every 2 to 3 months) and a double-blind randomized treatment period (for patients who had positive tests for *ESR1* variants and no evidence of radiologic or clinical disease progression) (Bidard et al. 2025). For the treatment period, eligible patients were randomly assigned to continue to receive CDK4/6 inhibitor and AI treatment or switched to camizestrant in combination with the same CDK4/6 inhibitor they were already receiving (Bidard et al. 2025). The primary outcome was investigator-assessed PFS, defined as the time from randomization until disease progression (as assessed according to RECIST, version

1.1) or death from any cause (Bidard et al. 2025). Key secondary outcomes were second PFS (defined as the time from randomization to the earliest of either subsequent disease progression after the next line of therapy or death) and OS (Bidard et al. 2025). Other secondary outcomes were objective response (complete response or partial response, as determined by the investigator according to RECIST) and safety (Bidard et al. 2025). Exploratory outcomes included patient reported global health status and quality of life, as measured by the European Organization for Research and Treatment of Cancer (EORTC) 30 item quality-of-life questionnaire, and patient reported vision related disturbances (e.g. photopsia- brief flashes of light in peripheral vision) and adverse events, as measured by the Visual Symptom Assessment Questionnaire (Bidard et al. 2025).

PASC agreed with the proposed outcomes in the draft PICO confirmation. PASC noted that the applicant will provide relevant data from SERENA-6 Clinical Study Report in the integrated codependent submission to PBAC and MSAC.

Assessment framework (for investigative technologies)

An initial assessment framework linking genetic testing for *ESR1* variants to the relevant health outcomes is presented in Figure 2.

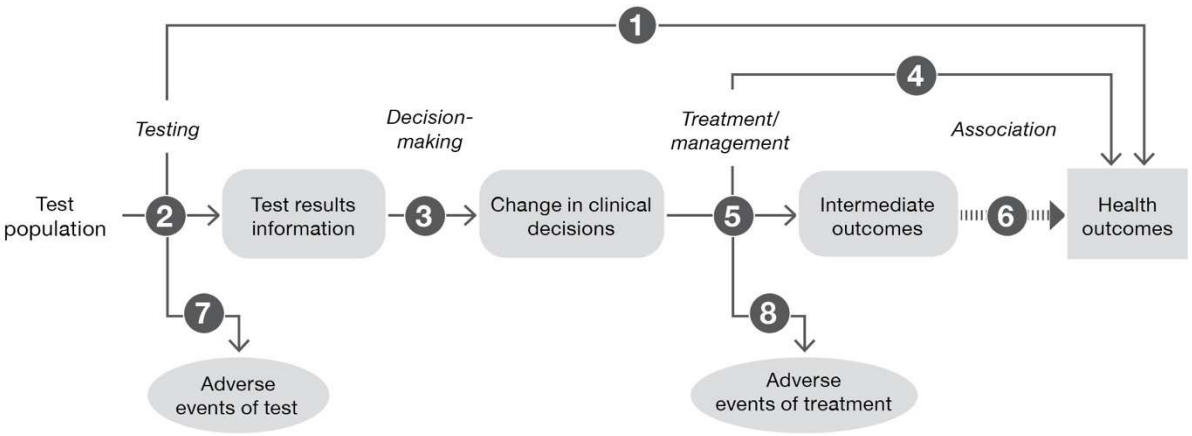

Figure 2 Generic assessment framework showing the links from the test population to health outcomes

Figure 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: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

Assessment questions for a claim of superiority:

1. Does the use of genetic testing for *ESR1* variants in place of no testing result in the claimed superior health outcomes?
2. What is the accuracy of NGS (sensitivity, specificity) using ctDNA extracted from blood (liquid biopsy)? How does this differ from ddPCR? What are the implications of discordance between these techniques?
3. Does the availability of new information (*ESR1* variants) lead to a change in management of the patient?

4. Do the differences in management derived from testing (switch from an AI to camizestrant in combination with a CDK4/6 inhibitor for patients with *ESR1* variants) result in the claimed superior health outcomes (PFS, OS, HRQoL)?
5. Do the differences in management derived from testing (camizestrant treatment for patients with *ESR1* variants) result in the claimed superior surrogate outcomes (objective response)?
6. Is the observed change in surrogate outcomes (objective response) associated with the concomitant change in claimed health outcomes (PFS, OS, HRQoL)? And how strong is the association?
7. What are the adverse events associated with testing for *ESR1* variants compared to a no testing strategy?
8. What are the adverse events associated with camizestrant treatment for patients with *ESR1* variants? What are the adverse events associated with SOC for patients without *ESR1* variants?

PASC did not raise any concerns with the proposed Assessment Framework.

Clinical management algorithms

Current clinical management algorithm (comparator)

The current clinical management algorithm for patients diagnosed with HR-positive HER2-negative locally advanced and metastatic breast cancer is shown in Figure 3. Australian clinical practice is informed by international treatment guidelines, including those from the US (National Comprehensive Cancer Network [NCCN] and the American Society of Clinical Oncology [ASCO]) and Europe (ESMO). Except for patients with visceral crisis (imminent organ failure) in whom chemotherapy is recommended, endocrine therapy plus a CDK4/6 inhibitor is the recommended SOC first-line treatment for patients with newly diagnosed HR+/HER2- locally advanced or metastatic breast cancer (Al Sukhun et al. 2024; Gennari et al. 2021; NCCN 2023). The choice of endocrine therapy is generally an AI, however for a small proportion of patients (primarily patients with primary endocrine therapy resistance or early relapse on/after adjuvant AI), fulvestrant is used. Patients who have received adjuvant CDK4/6 inhibitor in the early breast cancer setting are unable to be re-treated with a CDK4/6 inhibitor due to the current PBS once in a lifetime restriction and will therefore receive endocrine monotherapy or chemotherapy, depending on their disease characteristics.

Selection of second and subsequent lines of therapy is dependent on prior therapies used, disease aggressiveness, organ function, menopausal status and consideration of associated toxicities (Al Sukhun et al. 2024; Gennari et al. 2021; NCCN 2023). In general, sequential endocrine therapy with or without targeted therapies (CDK4/6 inhibitor if not used already, or everolimus) is recommended unless there is imminent organ failure (where chemotherapy is recommended), until all endocrine therapy options have been exhausted or where there is evidence of endocrine resistance (Al Sukhun et al. 2024; Gennari et al. 2021; NCCN 2023). Current PBS listed options for second line treatment include AIs (anastrozole, letrozole, and exemestane) or fulvestrant (if not already used in previous lines of therapy), everolimus-exemestane or tamoxifen. For patients with germline *BRCA 1/2* variants and no longer benefitting from endocrine therapy they may be offered a poly ADP ribose polymerase inhibitor (PARPi) rather than chemotherapy; chemotherapy may be offered if a PARPi is not available.

In recent times, novel therapies for endocrine-resistant tumours have entered clinical practice, utilising a biomarker-guided approach (Lloyd et al. 2024). In patients who relapse after SOC first-line treatment, ESMO guidelines recommend determination of somatic *PIK3CA* and *ESR1* variants, as well as germline *BRCA1/2* variants (Gennari et al. 2021). The MBS listing for genetic testing for germline *BRCA1/2* variants (MBS item number 73295) was recently expanded to include all patients with breast cancer, to determine eligibility for PBS-listed olaparib (a poly-ADP ribose polymerase [PARP] inhibitor) (DoHAC 2024). There have been MSAC applications for genetic testing for somatic *PIK3CA* (to determine eligibility for treatment with alpelisib [MSAC application 1604]) and *ESR1* variants (eligibility for elacestrant [MSAC application 1782]) after disease progression following first-line treatment for HR+/HER2- metastatic breast cancer. However, these co-dependent technologies are not currently listed on the MBS/PBS and only MSAC application 1782 advanced to MSAC consideration. At its April 2025 meeting MSAC did not support application 1782, primarily due to elacestrant not being supported by PBAC.

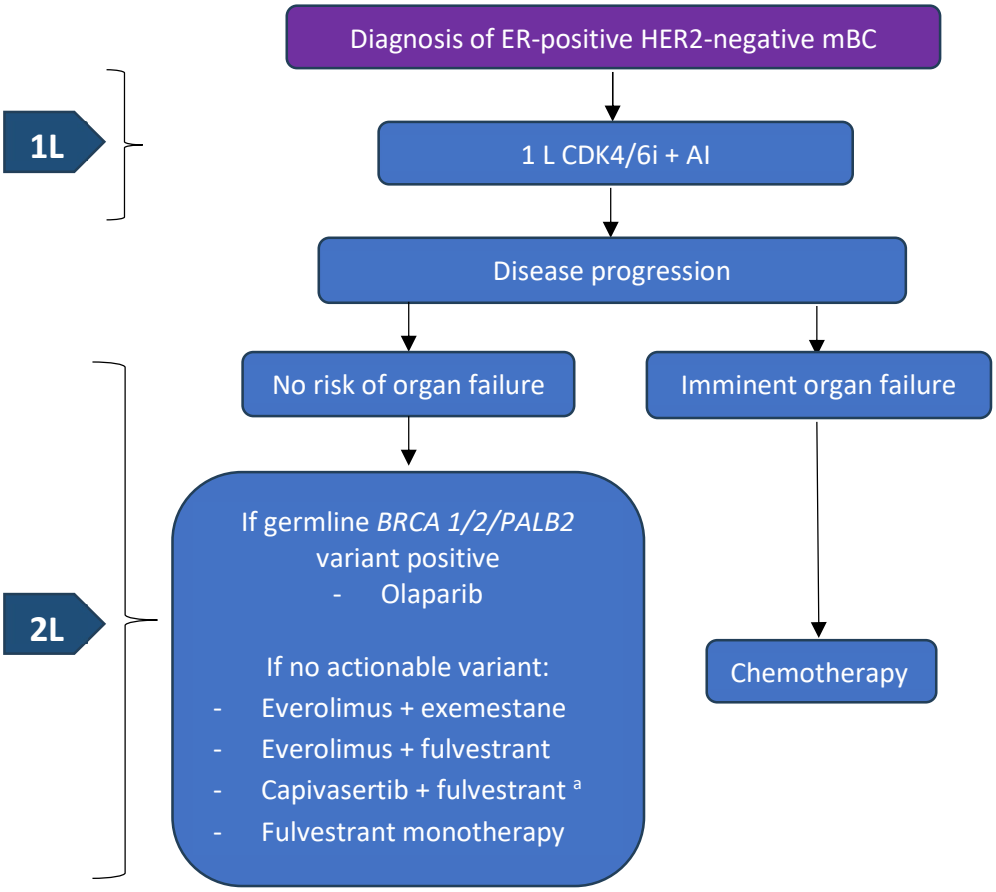

Figure 3 Current clinical management algorithm

1L = first line; AI = aromatase inhibitor; *BRCA1/2* = Breast cancer 1/2; CDK4/6i = cyclin dependent kinase 4/6 inhibitor; *ESR1* = estrogen receptor 1; ET = endocrine therapy; IV = intravenous; mBC = locally advanced or metastatic breast cancer; *PALB2* = partner and localiser of *BRCA 2*
[a] The PBS listing for capivasertib + fulverstrant recommends AKT pathway testing (where possible) for *PIK3CA*, *AKT1* and *PTEN* gene variants

PASC considered that the clinical management algorithm for current practice should be changed to specify that the patients eligible for testing are those diagnosed with ER-positive (not HR-positive) HER2-negative locally advanced or metastatic breast cancer. PASC noted that the clinical management algorithm for current practice was missing some relevant steps, including those for disease progression and criteria for 2L

treatment options (noting these were present in the proposed clinical management algorithm with the intervention developed by the assessment group Figure **4***).*

Proposed clinical management algorithm (intervention)

The proposed clinical management algorithm with the introduction of the co-dependent technologies is presented in **Error! Reference source not found.**. The key difference between the current algorithm and the proposed algorithm is that patients with HR+/HER2- locally advanced or metastatic breast cancer who have been treated with SOC first line treatment of an CDK4/6 inhibitor plus AI for at least 6 months, become eligible to be tested for *ESR1* variants every 2-3 months, at the same time as other routine testing. After a patient has tested positive for *ESR1* variants, they are eligible to receive PBS subsidised camizestrant in combination with the same CDK4/6 inhibitor they were receiving at the time of the testing.

This change will result in an increase in *ESR1* variant testing among all patients with locally advanced or metastatic breast cancer who commence first line treatment with a CDK4/6 inhibitor in combination with an AI, as well as a decrease in AI utilisation in patients who test positive for *ESR1* variants.

As noted earlier, some patients may require several tests before switching to camizestrant treatment (as *ESR1* variants develop over time), while others may receive multiple tests but receive no change in management (as approximately only 40%-50% of patients will acquire *ESR1* variants in response to first line therapy).

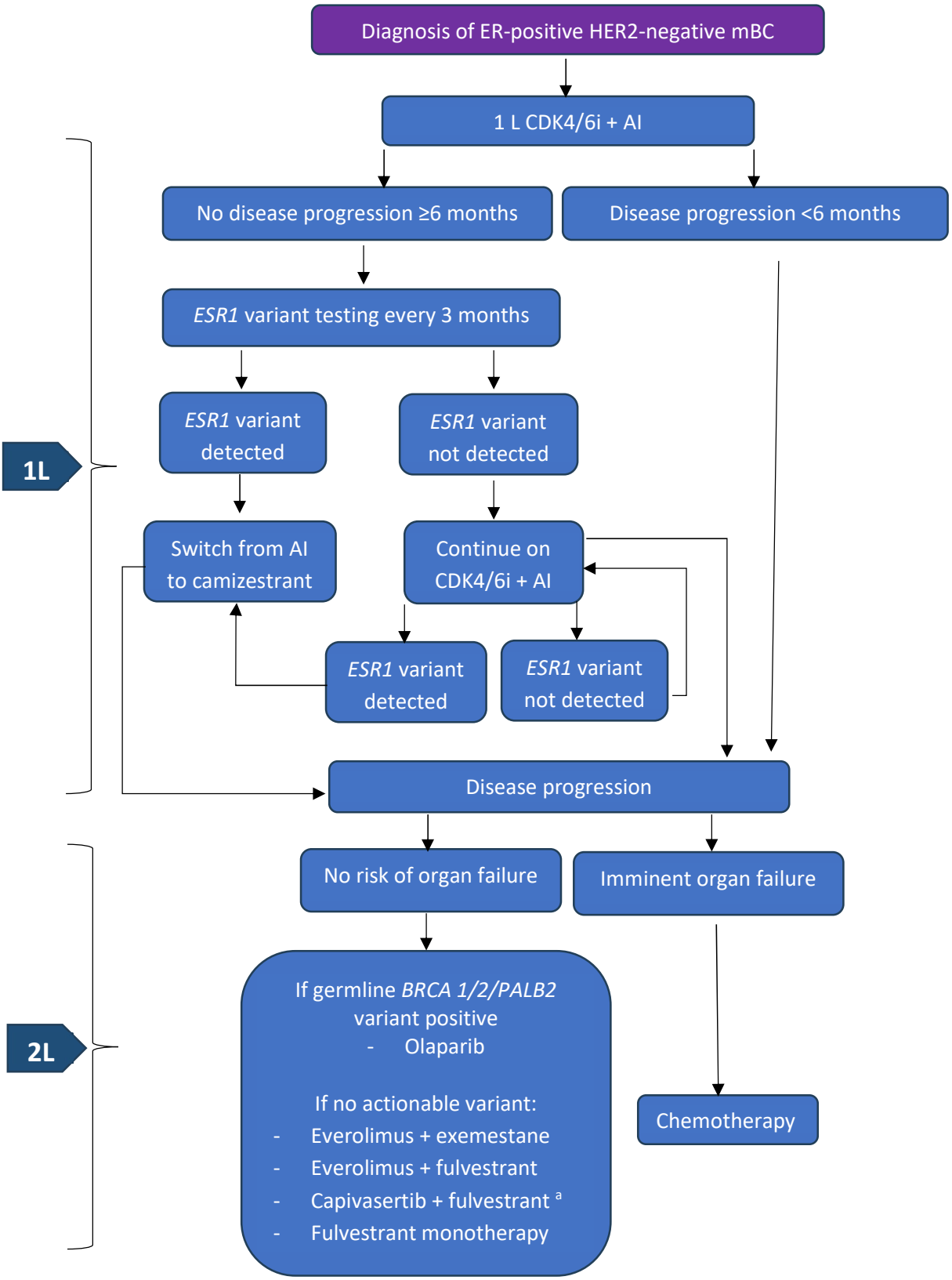

Figure 4 Proposed clinical management algorithm

1L = first line; AI = aromatase inhibitor; *BRCA1/2* = Breast cancer ½; CDK4/6i = cyclin dependent kinase 4/6 inhibitor; *ESR1* = estrogen receptor 1; ET = endocrine therapy; IV = intravenous; mBC = locally advanced or metastatic breast cancer; *PALB2* = partner and localiser of *BRCA 2*

[a] The PBS listing for capivasertib + fulverstrant recommends AKT pathway testing (where possible) for *PIK3CA*, *AKT1* and *PTEN* gene variants

PASC considered that the proposed clinical management algorithm (as suggested by the assessment group) was appropriate.

PASC queried the role that diagnostic imaging (based on the Australian diagnostic imaging guidelines) plays in this breast cancer population in current practice. PASC noted that in the SERENA-6 trial, radiological assessment was conducted using CT or MRI every eight weeks for the first 18 months, then every 12 weeks; this differs from Australian monitoring practice, which primarily relies on other modalities including CT, PET/CT and ultrasound, with MRI used where clinically indicated.

PASC queried whether this application raises a linked diagnostic imaging issue that requires further consideration. PASC noted that advice from the department is to await if PBS access requires formal radiographic confirmation of non-progression because existing MBS imaging services may be sufficient for radiographic assessment where clinically required. PASC noted that most patients are not expected to develop ESR1 *variants, so diagnostic imaging is important for indicating disease progression and when to stop* ESR1 *testing.*

Proposed economic evaluation

The overall clinical claim is that the proposed codependent technologies (genetic testing for *ESR1* variants and a switch from AI to camizestrant therapy in combination with a CDK4/6 inhibitor) results in superior health outcomes (improved PFS and HRQoL) compared to no testing and maintaining SOC first line treatment (AI in combination with a CDK4/6 inhibitor) in patients with HR+/HER2- locally advanced or metastatic breast cancer who have received at least 6 months of first line treatment with a CDK4/6 inhibitor in combination with an AI and whose disease has not progressed clinically or radiographically.

This claim is based on interim analysis results from the phase III clinical trial SERENA-6, which demonstrated that in patients with ER+/HER2- locally advanced or metastatic breast cancer who had received at least 6 months of first line therapy with an AI plus a CDK4/6 inhibitor, who did not have evidence of clinical or radiologic disease progression and tested positive for an *ESR1* variant, those that switched from an AI to camizestrant (in combination with the CDK4/6 inhibitor they were already receiving) had prolonged PFS compared to patients that maintained their SOC first line treatment (hazard ratio = 0.44, 95% CI 0.31-0.60, p=<0.001, median PFS 16.0 months vs 9.2 months) (Bidard et al. 2025). Additionally, the median time until a deterioration in the patient reported global health status and quality of life occurred was 21.0 months with camizestrant and 6.4 months with an AI (hazard ratio =0.54 95% CI 0.34-0.84, no p-value reported) (Bidard et al. 2025). The frequency of treatment discontinuation because of adverse events was 1.3% in the camizestrant arm compared to 1.9% in the control arm, while the incidence of serious adverse events was 10.3% in the camizestrant arm and 12.3% in the control arm (Bidard et al. 2025).

Based on the clinical claim and the available evidence, the appropriate type of economic evaluation would be a cost-effectiveness analysis/cost-utility analysis (Table 3).

Table 3 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of 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
? = reflect 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 the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

PASC noted that the applicant anticipates a claim of non-inferior safety; combined with the claim of superior health outcomes, PASC considered that a CEA/CUA is the appropriate type of economic evaluation.

PASC noted that the claim of superior health outcomes was based on an interim analysis from SERENA-6; where patients that switched from an AI to camizestrant had prolonged PFS (median PFS 16.0 months vs 9.2 months). PASC noted that the TGA evaluation for the clinical efficacy and safety of camizestrant is pending, while the applicant commented that they will provide PFS2 and safety data from the SERENA-6 Clinical Study Report at the integrated codependent submission to PBAC and MSAC. PASC noted that the primary analysis for OS is expected to be available REDACTED.

Proposal for public funding

The applicant did not provide a proposed MBS item descriptor in the PICO set. Proposed MBS item descriptors by the Department are presented in Table 4 (NGS) and Table 5 (dPCR).

Table 4 Proposed MBS item descriptor #1 by the department

Category 6 – Pathology Services	
MBS item AAAA	Group P7 - Genetics
Next generation sequencing (NGS) test of circulating tumour DNA (ctDNA) extracted from blood, in a patient with **ER-positive**, HER2-negative, locally advanced or metastatic breast cancer, as requested by a specialist or consultant physician, if the test is: a) to detect variants in ESR1 gene; and b) for a patient who has not previously tested and found to have an activating ESR1 variant; and c) to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme; and d) the test is not associated with a service to which item BBBB applies Applicable not more than **four** times in 12 months Fee: $1,200 Benefit: 75% = $900 85% = $1,095.50*	

PASC changes to the descriptor are in bold
*Greatest permissible gap (GPG) applies. As of 1 November 2025, GPG is $104.50

Table 5 Proposed MBS item descriptor #2 by the department

Category 6 – Pathology Services	
MBS item BBBB	Group P7 - Genetics
Digital PCR (dPCR) test of circulating tumour DNA (ctDNA) extracted from blood, in a patient with **ER-positive**, HER2-negative, locally advanced or metastatic breast cancer, as requested by a specialist or consultant physician, if the test is: a) to detect variants in ESR1 gene; and b) for a patient who has not previously tested and found to have an activating ESR1 variant; and c) to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme and d) the test is not associated with a service to which item AAAA applies Applicable not more than **four** times in 12 months Fee: $400 Benefit: 75% = $300 85% = $340	

PASC changes to the descriptor are in bold

Testing for *ESR1* variants is likely to be conducted in specialist laboratories which must hold the appropriate accreditation and registration for this testing procedure to receive MBS funding for the proposed test. Laboratories will need to participate in the relevant Royal College of Pathologist of Australasia (RCPA) Quality Assurance Program or a similar external quality assurance program. Testing must be conducted, and the results interpreted and reported by suitably qualified and trained molecular pathologists and anatomical pathologists.

The application did not propose an MBS fee, noting it is still to be confirmed but may be consistent with figures in the PICO for MSAC application 1782. In the pre-PASC meeting, the applicant indicated that the fee would depend on the testing methodology used and that they are currently liaising with pathology labs to determine an appropriate fee; early estimates are approximately $400 for ddPCR and $1200 for NGS.

The department noted that there were two different test methodologies proposed by the applicant for this service with differing fees. Therefore, the department has initially proposed two different items to reflect two item descriptors, test methodologies and fees.

PASC noted that there were two options for the MBS item descriptor:

Option A: Narrow, indication-specific descriptor

- *This option would retain wording closely tied to the proposed camizestrant setting*
- *It would provide tighter alignment to the current application but may require later amendment or a new application if another PBS-listed treatment requires* ESR1 *testing in a different setting*

Option B: Broader, future-proof descriptor

- *This option would remove treatment-line and non-progression requirements from the MBS item descriptor and rely on PBS restrictions to define the clinically eligible group for each relevant treatment*
- *It would also use drug-agnostic wording*

- *This would reduce the need for repeated MBS item redesign when new* ESR1*-linked treatments are listed*
- *This approach is consistent with recent co-dependent pathology MBS items supported by MSAC*

PASC also noted for the item descriptor for item BBBB, that a 'non-NGS method' encompasses dPCR and future-proofs the item.

PASC noted that MSAC previously considered testing every three months may be appropriate under application 1782 (genetic testing for ESR1 *variants to determine eligibility for PBS subsidised elacestrant).*

Overall PASC recommended broader future-proofed item descriptors for proposed MBS items AAAA and BBBB. PASC noted that the evidence for the available tests for both testing methodologies (NGS and dPCR) is still to be presented later in the integrated codependent submission per the applicant, and would impact the items, item descriptors and fees.

Regarding fees, PASC noted that the applicant had proposed that the MBS item should be priced at $1,700 for both NGS and dPCR from feedback from REDACTED and REDACTED. However, PASC also noted the following similar tests in Australia:

For item AAAA:

- *LifeStrands offers ctDNA* ESR1 *NGS (using a DNA panel of 34 genes) for $1200*
- *Australian Clinical Laboratories offers ctDNA tests for lung cancer, colorectal cancer and melanoma for testing 2-4 genes at $550. The Department noted that Australian Clinical Laboratories provides three different platforms for its ctDNA testing, namely NGS, Mass Array Agena Biosciences ULTRASeek and dPCR.*

For item BBBB, PASC noted the following similar tests available in Australia:

- *PathWest of Western Australia at QE II Medical Centre offers a dPCR ctDNA test for specific variants, $362.59*

PASC considered that ultimately the testing fees should be set at levels such that the combination of testing and treatment would still be cost-effective and also be supported using real world examples that accurately reflect the rapidly developing capabilities and cost-efficiencies of genetic testing providers in Australia.

Camizestrant is currently undergoing TGA evaluation for the proposed indication:

<u>Advanced breast cancer upon emergence of ESR1 mutation during first-line endocrine-based therapy</u>

Camizestrant in combination with a CDK4/6 inhibitor is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer upon emergence of ESR1 mutation during first-line endocrine-based therapy.

Summary of public consultation input

PASC noted and welcomed consultation input from 3 organisations and no individual input was received. The 3 organisations that submitted input were:

- Breast Cancer Network Australia (BCNA)
- Public Pathology Australia
- The Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP)

Consultation input was supportive of public funding for genetic testing to detect *ESR1* variants in patients with HR+/HER2- locally advanced or metastatic breast cancer to determine eligibility for treatment with PBS-subsidised camizestrant.

Consumer Experience

BCNA stated that metastatic breast cancer has profound and ongoing impacts on individuals, families and carers. Consumers living with metastatic breast cancer frequently experience physical impacts, emotional distress, disruption to employment and financial stability, and the burden of navigating complex treatment decisions. BCNA also stated that consumers consistently tell them that maintaining time on effective treatment and delaying disease progression is critical to preserving quality of life and independence.

Benefits and Disadvantages

The main benefits of public funding reported in the consultation input included improved access to *ESR1* variant testing and the potential for earlier identification of treatment resistance. BCNA stated that benefits also included less invasive blood-based ctDNA testing compared to tissue biopsy, and that camizestrant could be administered orally rather than intravenously. Public funding was also considered important to reduce out-of-pocket costs and support equitable access.

There were no disadvantages of public funding reported in the consultation input.

Population, Comparator (current management) and Delivery

The consultation input agreed with the proposed population, with BCNA stating that the population appropriately reflects those most likely to benefit from earlier identification of *ESR1* variants.

The consultation input agreed with the proposed comparator of no *ESR1* testing, noting testing is not currently MBS funded for this purpose.

MBS Item Descriptor and Fee

The consultation input largely agreed with the proposed service descriptor. Public Pathology Australia recommended the use of digital PCR (dPCR) rather than specifying droplet digital PCR (ddPCR) testing. BCNA supported a treatment agnostic testing item for *ESR1* variant testing for access to a relevant PBS-funded treatment, rather than specifying camizestrant.

The consultation input was supportive of the proposed service fee, with Public Pathology Australia stating that the proposed fee range was reasonable given the variation in testing methodologies**.**

Additional Comments

The RCPAQAP stated that a relevant external quality assurance program is available.

PASC noted that BCNA were supportive of the item, as they believe that the test would support patient access, equity and outcomes, and that the item would support access to precision oncology. PASC noted BCNA also suggested that the service be drug agnostic.

PASC noted that Public Pathology Australia were supportive of the item and suggested changing the term ddPCR to the broader dPCR.

PASC noted that The Royal College of Pathologists Australia Quality Assurance Programs (RCPAQAP) noted the EMQN quality assurance program for this test.

Next steps

PASC noted that the applicant will be lodging the integrated codependent submission in October 2026 for PBAC/MSAC consideration in March 2027.

Applicant Comments on Ratified PICO

The applicant had no comment.

References

Al Sukhun, S., Temin, S., Barrios, C. H., Antone, N. Z., Guerra, Y. C., Chavez-MacGregor, M., Chopra, R., Danso, M. A., Gomez, H. L., Homian, N. M., Kandil, A., Kithaka, B., Koczwara, B., Moy, B., Nakigudde, G., Petracci, F. E., Rugo, H. S., El Saghir, N. S., & Arun, B. K. (2024). Systemic Treatment of Patients With Metastatic Breast Cancer: ASCO Resource–Stratified Guideline. *JCO Global Oncology*, (10), e2300285. https://doi.org/10.1200/GO.23.00285

Australian Government, Department of Health and Aged Care. (2024). *Diagnostic Imaging Services Table Changes from 1 November 2024*. https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/1B8BCE241112BFA9CA258B8D000A497B/$File/PDF%20Version%20-%20Diagnostic%20Imaging%20Services%20Table%20Changes%20from%201%20November%202024.pdf

Australian Institute of Health and Welfare (AIHW). (2025, October 8). *Cancer data in Australia, Cancer incidence and survival by stage data visualisation*. https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-incidence-survival-stage-data-visualisation

Bidard, F.-C., Hardy-Bessard, A.-C., Dalenc, F., Bachelot, T., Pierga, J.-Y., de la Motte Rouge, T., Sabatier, R., Dubot, C., Frenel, J.-S., Ferrero, J. M., Ladoire, S., Levy, C., Mouret-Reynier, M.-A., Lortholary, A., Grenier, J., Chakiba, C., Stefani, L., Plaza, J. E., Clatot, F., … PADA-1 investigators. (2022). Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): A randomised, open-label, multicentre, phase 3 trial. *The Lancet. Oncology*, *23*(11), 1367–1377. https://doi.org/10.1016/S1470-2045(22)00555-1

Bidard, F.-C., Mayer, E. L., Park, Y. H., Janni, W., Ma, C., Cristofanilli, M., Bianchini, G., Kalinsky, K., Iwata, H., Chia, S., Fasching, P. A., Brufsky, A., Nowecki, Z., Pascual, J., Moreau, L., Chen, S.-C., Karadurmus, N., Gal-Yam, E. N., Jung, K. H., … Turner, N. C. (2025). First-Line Camizestrant for Emerging ESR1-Mutated Advanced Breast Cancer. *New England Journal of Medicine*, *393*(6), 569–580. https://doi.org/10.1056/NEJMoa2502929

Brett, J. O., Spring, L. M., Bardia, A., & Wander, S. A. (2021). ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Research: BCR*, *23*(1), 85. https://doi.org/10.1186/s13058-021-01462-3

Burstein, H. J., DeMichele, A., Somerfield, M. R., Henry, N. L., & for the Biomarker Testing and Endocrine and Targeted Therapy in Metastatic Breast Cancer Expert Panels. (2023). Testing for ESR1 Mutations to Guide Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update. *Journal of Clinical Oncology*, *41*(18), 3423–3425. https://doi.org/10.1200/JCO.23.00638

Cancer Australia. (2019). *Relative survival by stage at diagnosis (female breast cancer) | National Cancer Control Indicators*. https://ncci.canceraustralia.gov.au/relative-survival-stage-diagnosis-female-breast-cancer

Cancer Australia. (2025). *Breast cancer in Australia statistics*. https://www.canceraustralia.gov.au/cancer-types/breast-cancer/breast-cancer-australia-statistics

Davidson, B. A., Croessmann, S., & Park, B. H. (2021). The breast is yet to come: Current and future utility of circulating tumour DNA in breast cancer. *British Journal of Cancer*, *125*(6), 780–788. https://doi.org/10.1038/s41416-021-01422-w

Department of Health and Aged Care (DoHAC). (2024). *Expansion of germline variant testing item for patients with HER2 negative breast cancer*. https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/0633A695B50C08ECCA258B3400170349/$File/PDF%20-%20Expansion%20of%20germline%20variant%20testing%20item%20for%20patients%20with%20HER2%20negative%20breast%20cancer.pdf

Gennari, A., André, F., Barrios, C. H., Cortés, J., de Azambuja, E., DeMichele, A., Dent, R., Fenlon, D., Gligorov, J., Hurvitz, S. A., Im, S.-A., Krug, D., Kunz, W. G., Loi, S., Penault-Llorca, F., Ricke, J., Robson, M., Rugo, H. S., Saura, C., … ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. (2021). ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, *32*(12), 1475–1495. https://doi.org/10.1016/j.annonc.2021.09.019

Guardant Health. (2025). *Guardant360-CDx-Technical-Information-US*. https://www.guardantcomplete.com/assets/pdf/Guardant360-CDx-Technical-Information-US.pdf

Harbeck, N., Penault-Llorca, F., Cortes, J., Gnant, M., Houssami, N., Poortmans, P., Ruddy, K., Tsang, J., & Cardoso, F. (2019). Breast cancer. *Nature Reviews Disease Primers*, *5*(1), 66. https://doi.org/10.1038/s41572-019-0111-2

Liao, H., Huang, W., Pei, W., & Li, H. (2020). Detection of ESR1 Mutations Based on Liquid Biopsy in Estrogen Receptor-Positive Metastatic Breast Cancer: Clinical Impacts and Prospects. *Frontiers in Oncology*, *10*, 587671. https://doi.org/10.3389/fonc.2020.587671

Lloyd, M. R., Jhaveri, K., Kalinsky, K., Bardia, A., & Wander, S. A. (2024). Precision therapeutics and emerging strategies for HR-positive metastatic breast cancer. *Nature Reviews Clinical Oncology*, *21*(10), 743–761. https://doi.org/10.1038/s41571-024-00935-6

Najim, O., Papadimitriou, K., Broeckx, G., Huizing, M., & Wiebren, T. (2023). Validation of liquid biopsy for ESR1-mutation analysis in hormone-sensitive breast cancer: a pooled meta-analysis. *Frontiers in Oncology,* 13:1221773. https://doi: 10.3389/fonc.2023.1221773

National Cancer Institute. (2025). *Female Breast Cancer Subtypes—Cancer Stat Facts*. SEER. https://seer.cancer.gov/statfacts/html/breast-subtypes.html

NCCN. (2023). *NCCN Guidelines® Insights: Breast Cancer, Version 4.2023 in: Journal of the National Comprehensive Cancer Network Volume 21 Issue 6 (2023)*. https://jnccn.org/view/journals/jnccn/21/6/article-p594.xml

Popović, L., Borštnar, S., Božović-Spasojević, I., Cvetanović, A., Dedić Plavetić, N., Kaneva, R., Konsoulova, A., Matos, E., Tomić, S., & Vrdoljak, E. (2025). Treatment Sequencing in Metastatic HR+/HER2− Breast Cancer: A Delphi Consensus. *Cancers*, *17*(9), 1412. https://doi.org/10.3390/cancers17091412

Raei, M., Heydari, K., Tabarestani, M., Razavi, A., Mirshafiei, F., Esmaeily, F., Taheri, M., Hoseini,A., Nazari, H., Shamshirian, D. & Alizadeh-Navaei, R. (2024). Diagnostic accuracy of ESR1 mutation detection by cell-free DNA in breast cancer: a systematic review and meta-analysis of diagnostic test accuracy. *BMC Cancer,* 24:908. https://doi.org/10.1186/s12885-024-12674-z

Redig, A. J., & McAllister, S. S. (2013). Breast cancer as a systemic disease: A view of metastasis. *Journal of Internal Medicine*, *274*(2), 113–126. https://doi.org/10.1111/joim.12084

Turner, N. C., Kingston, B., Kilburn, L. S., Kernaghan, S., Wardley, A. M., Macpherson, I. R., Baird, R. D., Roylance, R., Stephens, P., Oikonomidou, O., Braybrooke, J. P., Tuthill, M., Abraham, J., Winter, M. C., Bye, H., Hubank, M., Gevensleben, H., Cutts, R., Snowdon, C., … Ring, A. (2020). Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): A multicentre, multicohort, phase 2a, platform trial. *The Lancet Oncology*, *21*(10), 1296–1308. https://doi.org/10.1016/S1470-2045(20)30444-7