Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1782 – Genetic testing to detect estrogen receptor 1 (ESR1) variants in patients with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, to determine eligibility for treatment with PBS subsidised elacestrant

Applicant: **A. Menarini Pty Ltd.**

Date of MSAC consideration: **3-4 April 2025**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of the application

An integrated codependent application was received from A. Menarini Pty Ltd by the Department of Health and Aged Care. The application requested:

- Medicare Benefits Schedule (MBS) listing of next generation sequencing (NGS) testing for activating estrogen receptor 1 (*ESR1*) variants in circulating tumour deoxyribonucleic acid (ctDNA) extracted from blood plasma (liquid biopsy) to determine eligibility for treatment with elacestrant in postmenopausal women or men with estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-), locally advanced or metastatic breast cancer (mBC), who have disease progression following at least one line of endocrine therapy (ET), including a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i); and
- Pharmaceutical Benefits Scheme (PBS) General Schedule Authority Required (telephone/online) listing of elacestrant for the treatment of ER+/HER2- locally advanced or mBC with disease progression following at least one line of ET, including a CDK4/6i, in patients whose tumours have evidence of activating *ESR1* variants.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of genetic testing to detect estrogen receptor 1 (*ESR1*) variants in circulating tumour DNA (ctDNA) to determine eligibility for Pharmaceutical Benefits Scheme (PBS) subsidised elacestrant treatment in patients with estrogen receptor positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) locally advanced or metastatic breast cancer. MSAC noted that the PBAC did not recommend PBS listing of elacestrant at its March 2025 meeting. MSAC considered that patients whose tumours have *ESR1* variants may benefit more from elacestrant treatment. However, MSAC noted that PBAC considered the clinical benefit for elacestrant in the pivotal trial was likely overestimated due to the inappropriate comparator. MSAC noted that testing would be repeated in patients who previously tested negative, and considered that the proposed MBS listing if supported would result in substantial budget impact to the MBS. MSAC noted that this

was the first time it had considered *ESR1* testing in ctDNA, which is extracted from blood, and policy and implementation issues that need to be addressed for any future applications.

Consumer summary

This is a co-dependent application from A. Menarini Australia Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of genetic testing to detect estrogen receptor 1 (*ESR1*) variants in patients with estrogen receptor (ER)-positive, *HER2*-negative, locally advanced or metastatic breast cancer, so that they can access the medication elacestrant on the Pharmaceutical Benefits Scheme (PBS). While MSAC considered the testing, the Pharmaceutical Benefits Advisory Committee (PBAC) considered the medicine for listing on the PBS.

Breast cancer is the abnormal growth of cells in the glands, ducts or tissues of the breast. Breast cancer is referred to as 'advanced' once it has spread locally (to tissues around the breast, such as skin and nearby lymph nodes, called locally advanced) or spread from the original location to a new location in the body (away from the breast, such as bones or liver, called metastatic). Most breast cancers are 'hormone receptor positive'. This means the cancer cells have hormone receptors on them and need hormones to grow and reproduce. ER stands for '(o)estrogen receptor' (a type of hormone receptor) and HER2 stands for 'human epidermal growth factor receptor 2'. ER-positive and HER2-negative are receptor subtypes of breast cancer. Finding out which subtype someone's cancer is helps with predictions about how the cancer may respond to treatment.

Further, some people with breast cancer might have alterations in the genetic code of their cancer cells. These alterations can change how the cancer cells respond to certain medicines. One type of genetic alteration is variations in the *ESR1* gene. In some people this can mean their cancer will not respond to endocrine therapy, a common treatment. They will need different treatments. This application to MSAC proposed using genetic testing to detect variations to the *ESR1* gene in breast cancer using tumour DNA (ctDNA) extracted from blood plasma. ctDNA is DNA that has been released from cancer cells and is circulating in the bloodstream. Using ctDNA instead of tumour tissue for genetic testing means patients can have a blood test instead of a biopsy. If the person has certain variants detected (positive test result), they would be eligible to have a treatment called elacestrant.

MSAC did not support *ESR1 testing.* MSAC and PBAC had considered that there was not enough evidence to be certain that elacestrant can benefit people who test positive, over and above the interventions currently available. MSAC noted that the genetic test used in the clinical research study of elacestrant is not available in Australia and there are currently not enough accredited laboratories to offer the test.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support MBS listing of *ESR1* testing in patients with breast cancer to determine eligibility for elacestrant. MSAC considered that, since the PBAC did not support listing elacestrant on the PBS (the medicine that would be initiated if *ESR1* variants were detected), there was no need for *ESR1* testing at present.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this was a co-dependent application from A. Menarini Australia Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of genetic testing for activating estrogen receptor 1 (*ESR1*) variants in circulating tumour deoxyribonucleic acid (ctDNA) extracted from blood plasma (liquid biopsy), to determine eligibility for treatment with elacestrant in postmenopausal women or men with estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-), locally advanced or metastatic breast cancer (mBC), who have disease progression following at least one line of endocrine therapy (ET), including a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). The application also requested Pharmaceutical Benefits Scheme (PBS) listing of elacestrant for those patients whose tumours had evidence of activating ESR1 variants.

MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend elacestrant at its March 2025 meeting. MSAC noted that the PBAC considered that in the heavily pre-treated population included in the clinical trial for elacestrant, the control arm of fulvestrant was inappropriate for many patients, and was not representative of standard of care (SOC). The PBAC considered the outcomes from that the pivotal trial are likely to overestimate the clinical benefit for elacestrant due to the inappropriate comparison. The PBAC did not consider elacestrant cost-effective at the proposed substantially higher cost and advised that a resubmission may be lodged using the standard re-entry pathway.

MSAC noted that breast cancer is the second most diagnosed cancer and the fifth most common cause of cancer-related death in Australia. Early stages of breast cancer are treated with surgery and/or systemic therapy. Around 20–30% of cases progress to mBC, and around 5–10% of cases are mBC at diagnosis. Around 70% of mBCs are ER+/*HER2*– tumours. SOC for first-line treatment of mBC is endocrine therapy (with either aromatase inhibitors or fulvestrant) and CDK4/6i. *ESR1* variants are a key mechanism of endocrine therapy resistance, and are acquired by around 40–50% of ER+/*HER2*– mBC after first-line treatment, but can continue to emerge at each episode of disease progression. More than 20 different *ESR1* variants have been described.

MSAC noted that the proposed test procedure involves testing ctDNA from a peripheral blood sample, also known as a liquid biopsy. MSAC considered that the proposed use of ctDNA testing rather than tumour tissue testing was appropriate. Because mBC is heterogenous and *ESR1* variants may be acquired, and there may be numerous tumour sites, multiple tissue biopsies would be required at each stage of disease progression. MSAC considered that ctDNA would be more indicative of active tumour sites and would limit the impact of biopsy on patients.

MSAC noted that while the applicant proposed using NGS for *ESR1* testing, digital droplet polymerase chain reaction (ddPCR) may be appropriate as an alternative test methodology. Other suitable methodologies may also become available in the future. MSAC noted that while ddPCR has greater sensitivity than NGS and is cheaper (in a high volume laboratory), multiple assays would be required to cover all known *ESR1* variants. MSAC considered that, in practice, laboratories would be unlikely to develop a bespoke ddPCR assay for every variant but rather use an NGS approach. MSAC therefore considered that the MBS item descriptor for *ESR1* testing should be method-agnostic.

As for the proposed MBS fee of $1,500, MSAC considered that it was appropriate, as it is in alignment with an NGS approach and laboratories would be unlikely to use ddPCR in practice. MSAC noted the Pre-Committee Response reported that all laboratories contacted by the applicant would either not offer the test if the MBS rebate was inadequate, or would introduce a patient copayment, resulting in equity or access issues.

MSAC noted that the Guardant360 assay used in the pivotal trial is not available in Australia and that there are no ctDNA *ESR1* tests listed on the Australian Register of Therapeutic Goods (ARTG). MSAC also noted the Pre-Committee Response reported that 2 Australian laboratories are in the process of obtaining accreditation with the National Association of Testing Authorities (NATA) to perform *ESR1* testing using ctDNA, but no Australian laboratories are currently accredited for this testing. MSAC therefore queried if the current capacity to offer *ESR1* testing is adequate in Australia.

MSAC welcomed consultation input from 2 non-consumer organisation and 4 consumer organisations, and noted that the feedback was broadly supportive of the application. MSAC noted that some feedback raised concerns around equity and access because genetic testing services are located in metropolitan areas. However, MSAC considered that ctDNA specimens are easier to collect and transport than tissue specimens in rural and remote areas, which may help to increase access for rural and remote patients.

MSAC noted the applicant claimed that, for those who test positive for an *ESR1* variant, elacestrant is superior to SOC in terms of clinical effectiveness and with a different, but manageable, safety profile.

MSAC agreed with the ESCs that the safety claim was not appropriate, and that elacestrant treatment has inferior safety compared to the comparator (SOC). While the test itself is of low-risk and minimally invasive, treatment-related adverse events arising from a change in management to elacestrant involve a greater risk than SOC for all adverse events ≥Grade 3, including those resulting in treatment interruption. In terms of clinical effectiveness, MSAC noted that PBAC did not consider the evidence presented supported clear survival benefits with elacestrant treatment over SOC. MSAC agreed with PBAC's concerns and considered that the clinical claim of superior effectiveness was not supported.

MSAC noted the ESCs' concerns about the claim of co-dependency, as the predictive value of *ESR1* as a biomarker was uncertain. MSAC considered that there was biological plausibility for co-dependence, but noted that the test for interaction between *ESR1* and non-*ESR1* variant subgroups in the pivotal trial was not significant for *ESR1* variant status. MSAC considered that, overall, the claim of co-dependency was reasonable, but that the extent of treatment benefit was uncertain.

MSAC noted that the applicant presented a cost-utility analysis. MSAC noted concerns raised by the ESCs, and agreed that the incremental cost-effectiveness ratio (ICER) had likely been underestimated due to several inappropriate assumptions. MSAC considered that the assumptions regarding 100% test accuracy and 0% test failure rate were not reasonable. While MSAC noted the applicant's Pre-Committee Response stated these assumptions were in line with the pivotal trial, MSAC considered the assumptions unlikely to reflect rates in practice with real-world populations. MSAC also noted that the economic analysis assumed that patients were only tested once per lifetime, despite the proposed MBS item descriptor allowing for testing at each stage of disease progression. MSAC further noted that the economic analysis included the *ESR1*-positive group only (not the overall test population). MSAC noted that additional sensitivity analyses had been performed to factor in potential retesting rates, with minimal impact on the ICER, as the ICERs were primarily driven by the cost of elacestrant. MSAC noted that PBAC did not consider elacestrant treatment to be cost-effective.

MSAC noted the financial and budgetary impacts, including the additional sensitivity analyses requested by the ESCs using alternative test costs (e.g. in line with ddPCR costs). The net cost to the MBS was estimated at between $0 to < $10 million and $20 million to < $30 million, depending on the cost of the test and the prevalence of activating *ESR1* variants. MSAC noted the ESCs' advice that testing should be restricted to once every 6 months in patients with a

previous negative result. However, MSAC considered that testing every 3 months might be a more appropriate timepoint for retesting, noting that this would increase the financial estimates. MSAC advised that there should be no further *ESR1* testing following a positive result.

MSAC considered that there is no basis to support *ESR1* variant testing, as the PBAC did not recommend the proposed PBS listing of elacestrant. MSAC advised that a resubmission should address the magnitude of clinical benefit with an appropriate comparator and the implementation issues related to the provision of ESR1 testing. MSAC considered the resubmission would need to be an integrated codependent submission and be re-considered by the ESCs.

4. Background

This is the first time the Medical Services Advisory Committee (MSAC) has been requested to consider the proposed testing for *ESR1* variants in ctDNA extracted from blood (liquid biopsy) (either alone or as part of a co-dependent submission).

MSAC's PICO Advisory Subcommittee (PASC) considered, in August 2024, another application (MSAC application 1783) that requested public funding for ctDNA or tumour testing (using NGS) to detect *PIK3CA* variants in patients with HR+/HER2– locally advanced or mBC whose disease progressed during or within 12 months of completing adjuvant ET, to determine eligibility for treatment with PBS subsidised inavolisib.

5. Prerequisites to implementation of any funding advice

Test

The submission provided a list of assays available in Australia that could potentially be used to detect *ESR1* variants in liquid biopsy samples (Table 1). However, none of these assays were TGA-registered at the time of evaluation.

Table 1: Analytic specifications of assays available in Australia

Company	Assay Name	Type of assay	LoD[a] (% VAF) (limit of detection)	Sensitivity	Specificity
Thermofisher	Oncomine Breast cfDNA [b]	NGS to detect mutations in 20 genes (incl. *ESR1*)	0.1% (1 mutant copy in a background of 1000 wildtype copies)	~80%	>99%
Thermofisher	Oncomine Precision GX [c]	NGS to detect mutations in 45 genes (incl. *ESR1*)	0.33%	89.2%	>99%
Roche	Avenio ctDNA expanded v2 [d]	NGS to detect mutations in 77 genes (incl. *ESR1*)	0.5% at 50 ng DNA input. Can report down to 0.1% with lower sensitivity	> 99%	>99%
Illumina	Illumina TruSight 500 Oncology ctDNA [e]	NGS to detect mutations in 523 cancer genes incl. *ESR1*	Detecting SNVs at or above 0.5% VAF at input of 30 ng ctDNA.	>99%	>99%
Guardant Health Inc (US)	Guardant360® CDx [f]	NGS to detect mutations in tumour genes including *ESR1*	≥1.8%; *1.1% MAF* (50 ng cfDNA) ≥0.2%; *0.3% MAF* (30 ng cfDNA)	98% (PPA)	85% (NPA)

Source: Table 1.6: Analytic specifications of assays available in Australia and added to during the evaluation using data from the submission.

ctDNA = circulating tumour DNA; DNA = deoxynucleic acid; *ESR1* = estrogen receptor 1; GX =gene assay ; LoD = limit of detection; ng =nanograms; MAF = mutant allele fraction ;NGS = next generation sequencing; NPA = negative percent agreement; PPA = positive percent agreement; SNV = single nucleotide variant; VAF = variant allele fraction.

[a] LoD is defined as the lowest variant level that can be detected at least 95% of the time. The VAF for *ESR1* mutations was measured using sample pools from *ESR1*m positive breast cancer samples and was established for the following *ESR1* mutations: E380Q, Y537S, D538G.

[b] https://www.thermofisher.com/order/catalog/product/A35865

[c] https://www.thermofisher.com/ch/en/home/clinical/preclinical-companion-diagnostic-development/oncomine-oncology/oncomine-precision-assay.html

[d] https://sequencing.roche.com/global/en/products/group/avenio-ctdna-expanded-kits.html

[e] https://aacrjournals.org/cancerres/article/80/16_Supplement/3114/642448/Abstract-3114-Analytical-validation-of-Illumina-s

[f] Guardant Health does not explicitly state sensitivity and specificity, but PPA and NPA to their comparator method "Agena Ultra Seek" from Agena Bioscience

The submission stated that testing is expected to be conducted in specialist laboratories with the appropriate accreditation and registration and as part of the Royal College of Pathologists of Australasia (RCPA) Quality Assurance Program (RCPAQAP) or a similar external quality assurance program. Results would need to be interpreted and reported by suitably qualified and trained molecular pathologists.

The PASC-ratified PICO Confirmation noted the lack of RCPAQAP for ctDNA testing and queried how this would affect the proposed ctDNA testing. PASC noted the RCPAQAP partnered with the European Molecular Genetics Quality Network (EMQN) for the provision of its External Quality Assessments (EQA). Additionally, PASC noted that the EMQN ran a pilot EQA scheme in early 2024 for breast cancer *ESR1* testing in plasma. PASC noted that multiple Australian diagnostic laboratories participate in the EMQN EQA scheme. The submission advised that it has initiated contact with the RCPA to discuss details of a potential QAP in Australia (p7, 1782 Ratified PICO Confirmation, August 2024 PASC meeting).

The submission stated that it is striving to facilitate *ESR1* testing in ctDNA extracted from blood (liquid biopsy) by leveraging established pathology laboratories (National Association of Testing Authorities [NATA] accredited) across the country as reference labs for genomic testing. To achieve this goal, the submission reported the initiation of the following activities:

- Building infrastructure and ensuring technical readiness for *ESR1* variant testing in liquid biopsy.
- Implementing an External Quality Program (EQP) for *ESR1* variant testing in liquid biopsy.
- Raising awareness about *ESR1* variant testing in liquid biopsy.

The submission stated that the support for testing implementation in Australia is continual, through the provision of *ESR1* variant commercial positive reference controls and enrolment into an international EQA program to aid Quality Assurance and Testing Validation.

To ensure equitable access, a semi-centralised approach has been initiated redacted[1].

PASC noted that liquid biopsy was the preferred specimen type for *ESR1* variant testing but queried whether tissue biopsy would also need to be considered given many labs in Australia are not yet established for testing ctDNA from liquid biopsy. The submission advised that it was working closely with several laboratories in Australia to ensure they are appropriately equipped for testing of ctDNA from liquid biopsy, with two laboratories currently ready for testing and a further 3 laboratories expected to be ready by Q1/Q2 2025 (p7, 1782 Ratified PICO Confirmation, August 2024 PASC meeting).

A summary of current Australian laboratories with potential *ESR1* testing capabilities is presented in Table 2. Redacted[1].

Table 2: Australian laboratories with potential ESR1 testing capabilities

State	Institution	Current *ESR1* testing in LBx		Capability (NGS)		LBx expertise	
		Yes	No	Yes	No	Yes	No
Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
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	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
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	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
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	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted

Source: Table 1.9, p42 of the submission

Redacted; cfDNA = cell free deoxyribonucleic acid; **Redacted**; *ESR1* = estrogen receptor 1; LBx = liquid biopsy; NGS = next generation sequencing; **Redacted**

[a] LBx / NGS (**Redacted**)

[b] LBx / NGS (**Redacted**)

The commentary considered that, based on the information provided in the submission, it is unclear whether there is sufficient capacity in current Australian laboratories to meet testing requirements for *ESR1* variants in ctDNA.

[1] Information will be unredacted in full when the TGA Australian Public Assessment Report (AusPAR) is available.

Drug

The submission was made under the Therapeutic Goods Administration (TGA)/ Pharmaceutical Benefits Advisory Committee (PBAC) Parallel Process. **Redacted**[2].

Elacestrant was **redacted**[2].

6. Proposal for public funding

Test

The proposed test was NGS testing for *ESR1* variants in ctDNA extracted from blood plasma (liquid biopsy). The test sponsor was the submission applicant (clinical sponsor).

The submission stated that using NGS, the pathologist will be able to preselect the genes to identify - often referred to as a 'testing panel'. This presents the opportunity to test for multiple tumour biomarkers at once to help inform treatment decisions, including *ESR1, PIK3CA*, *BRCA1/2* and *PALB2*. Genetic testing for *BRCA1/2* and *PALB2* is currently listed on MBS (item 73297) while PASC has previously considered two applications for *PIK3CA* variant testing (application 1604 in December 2019[3] and application 1783 in August 2024[4]), although these applications have not yet progressed to or been considered by MSAC.

Oncologists would assess eligibility of patients for *ESR1* variant testing, draw a blood sample from the patient and send the sample to a clinical laboratory, or refer the patient to a clinical laboratory or collection point where a blood sample is drawn and samples are then sent to the clinical laboratory. 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.

The requested MBS item descriptor is presented in Table 3.

Table 3: Proposed MBS item descriptor in the submission

Category 6 – Pathology Services Group P7 - Genetics
Proposed item descriptor XXXXX Next generation sequencing (NGS) test for *ESR1* variants by ctDNA extracted from blood plasma from a patient with locally advanced or metastatic ER-positive, HER2-negative breast cancer. As requested by a specialist or consultant physician, to determine if requirements relating to *ESR1* variant status for access to estrogen receptor inhibitors under the Pharmaceutical Benefits Scheme are fulfilled.
Fee: $1,500.00 Benefit: 75% = $1,125 85% = $1,397.60

Source: Table 1.14, p57 of the submission

[2] Information will be unredacted in full when the product has been approved by the Therapeutic Goods Administration (TGA) and listed on the Australian Register of Therapeutic Goods (ARTG)

[3] MSAC 1604 - PIK3CA mutation testing for postmenopausal women or men with advanced breast cancer who have progressed during or following treatment with an aromatase inhibitor

[4] MSAC 1783 - Genetic testing to detect PIK3CA mutations in patients with hormone receptor (HR)-positive, HER-2 negative, locally advanced or metastatic breast cancer, to determine eligibility for treatment with PBS subsidised inavolisib

The commentary noted the proposed MBS item descriptor differed from the agreed descriptor in the MSAC PICO confirmation (Table 3, p17, 1782 Ratified PICO Confirmation, August 2024 PASC Meeting).

Firstly, the commentary noted that while the agreed descriptor was method-agnostic, the current proposed descriptor specifies that testing must use NGS. PASC noted the department preference for method agnostic items but considered that justification for test methodology specific items should be included in the assessment (p17, 1782 Ratified PICO Confirmation, August 2024 PASC Meeting). The commentary considered that the performance of NGS over alternative test methodologies (digital droplet polymerase chain reaction [ddPCR], quantitative polymerase chain reaction [qPCR]) was not adequately demonstrated in the submission (very limited evidence extraction, summary or synthesis was presented in the submission based on the identified literature such that it was unclear what conclusions could be drawn). In contrast, one of the few studies presented in any detail for this assessment, noted that while both ddPCR and NGS demonstrated high specificity (90.44% vs 90.14%, respectively), ddPCR outperformed NGS in terms of sensitivity (81.01% vs 56.78%)(Raei et al, 2024).

Secondly, the commentary noted that the agreed item descriptor specified that patients must have "locally advanced or metastatic ER-positive, HER2-negative breast cancer who has disease progression following at least one line of endocrine therapy, including a CDK 4/6 inhibitor". The commentary noted the current proposed MBS item descriptor does not specify "at least one line of endocrine therapy, including a CDK 4/6 inhibitor". However, the department advised that this information is not required for the MBS item descriptor, as long as it is specified in the PBS restriction.

Additionally, given testing is relevant at each episode of disease progression during the metastatic course, PASC considered it was appropriate to include a restriction for the limit/frequency of testing to be once every 6 months (p17, 1782 Ratified PICO Confirmation, August 2024 PASC Meeting). The commentary noted this has not been included in the proposed MBS item descriptor.

As a result of these differences, the commentary considered that the proposed MBS item descriptor may result in an eligible test population that is broader than that specified in the PICO confirmation.

In estimating the proposed MBS fee, the submission identified the following MBS listed NGS tests:

- Item 73437 for a nucleic acid-based multi-gene panel test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer has a fee of $1,247.00.
- Item 73438 for a DNA-based multi-gene panel test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer has a fee of $682.35.
- Item 73433 for an NGS test for Neurotrophic Tyrosine Receptor Kinase (NTRK) fusions by DNA or ribonucleic acid (RNA) in tumour tissue from a patient with a locally advanced or metastatic solid tumour has a fee of $1,000.00.
- Item 73310 for NGS testing of bone marrow or peripheral blood for the assessment of measurable residual disease in acute lymphoblastic leukaemia has a fee of $1,550. (NOTE: this is a test of cellular DNA, not cell-free DNA)

These items mostly use NGS from tissue biopsy. The submission noted that currently there is no MBS-listed item for NGS testing using ctDNA extracted from blood plasma (liquid biopsy).

The submission stated it also sought input from a pathologist on the cost of performing NGS testing for *ESR1* variants by ctDNA extracted from blood plasma. The submission stated the

advice received was that the depth of sequencing required for ctDNA is significantly higher than tissue testing to reach the required test performance characteristics to make it fit for purpose, and that the sequencing costs are higher to get to the desired outcome. Special collection tubes are also required to ensure stability of the ctDNA after the blood draw. Further, extraction of ctDNA is also more expensive; the cost is over twice that for tissue testing since different procedures and reagents are needed. Based on this information, the MBS fee proposed in the submission was $1,500.00. The commentary noted that this is higher than similar tests currently listed on the MBS, including testing for germline gene variants *BRCA1/2* and *PALB2* (MBS item 73296) and testing for variants known to be causative of childhood hearing loss using NGS (MBS items 73440, 73444), which are priced at $1,200.00 (page 17, 1782 Ratified PICO Confirmation, August 2024 PASC meeting).

Drug

The proposed drug was elacestrant indicated for the treatment of locally advanced or metastatic breast cancer with the proposed clinical criteria of HR+, HER2-, evidence of *ESR1* variant and patients must have received at least one prior line of endocrine therapy including a CDK4/6 inhibitor. The requested PBS restriction states that 'the condition must be hormone receptor positive', however the proposed TGA indication, the inclusion criteria for the key clinical trial, EMERALD, and the estimation of use in clinical practice for the financial impact specified that patients must be 'estrogen receptor positive'.

Table 4: Key components of the clinical issue addressed by the submission

Component	Description
Population	Test: Men and postmenopausal women with ER+/HER2- locally advanced or mBC, who have disease progression following at least one line of ET, including a CDK4/6i. Drug: Men and postmenopausal women with ER+/HER2- locally advanced or mBC, who have disease progression following at least one line of ET, including a CDK4/6i, and test positive for an *ESR1* variant.
Intervention	Test: Testing for *ESR1* variants in ctDNA extracted from blood (liquid biopsy) through NGS Drug: Elacestrant 345 mg po daily until disease progression or unacceptable toxicity
Comparator	Test: No testing Drug: SOC, consisting of conventional ET (monotherapy): • Fulvestrant 500 mg IM days 1 and 15 (cycle 1), then day 1 in subsequent cycles (frequency: 28 days), • Anastrozole 1 mg po daily, • Letrozole 2.5 mg po daily, or • Exemestane 25 mg po daily until disease progression or unacceptable toxicity.

Outcomes	Test:
	Diagnostic accuracy (Sensitivity, Specificity, PPV, NPV), test-retest reliability.
	Predictive validity of the test (distinguished from *ESR1* as a prognostic biomarker)
	Comparative performance of *ESR1* variant testing methods
	• Incremental benefits and risks of ctDNA testing compared to tumour testing for *ESR1* variants
	• Concordance between *ESR1* variant testing assays:
	  ○ NGS vs ddPCR
	  ○ NGS vs qPCR
	Change in clinical management from testing
	• Percentage of patients changing treatment plan
	• Impact of discordance between test methods on treatment selection and effect.
	Testing Safety outcomes
	• AEs related to testing
	
	Drug: OS, PFS, ORR, CBR, CR, PR, SD, HRQoL, treatment-emergent and treatment-related AEs

Clinical claim	In men and postmenopausal women with ER+/HER2- locally advanced or mBC, who have disease progression following at least one line of ET, including a CDK4/6i, and who test positive for an *ESR1* variant, elacestrant is superior to SOC in terms of effectiveness with a different and manageable safety profile.

Source: Table 1.1, p21 of the submission

AEs = adverse events; CDK4/6i = cyclin dependent kinase 4/6 inhibitors; CBR = clinical benefit rate; CR = complete response; ctDNA = circulating tumour DNA; ddPCR = digital droplet polymerase chain reaction; ER+/HER2- = estrogen receptor positive, human epidermal growth factor 2 negative; *ESR1* = estrogen receptor 1; ET = endocrine therapy; HRQoL = health-related quality of life; IM = intramuscular; mBC = metastatic breast cancer; mg = milligram; NGS = next-generation sequencing; ORR = overall response rate; NPV = negative predictive value; po = per oral; PPV = positive predictive value; PR = partial response; qPCR = quantitative polymerase chain reaction; OS = overall survival; PFS = progression-free survival; SD = stable disease; SOC = standard of care.

7. Population

Disease

Breast cancer is a common, molecularly heterogenous malignancy that causes high levels of disability and mortality and predominantly occurs in in postmenopausal women aged ≥50 years.

In Australia, it is the second most diagnosed cancer and the fifth most common cause of cancer death, with an estimated 20,640 new cases diagnosed and 3,214 deaths in 2022[5].

In the early stages of breast cancer, where the cancer is confined to the breast or axillary lymph nodes, the disease can be cured using surgery, usually with neoadjuvant or adjuvant systemic therapy[6]. However, some patients (5-10%) present with mBC at diagnosis (de novo metastatic disease), and many with early breast cancer eventually progress to mBC (20% to 30%) (recurrent metastatic disease)6.

While incurable, mBC is treatable, 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). Treatment choice depends on the histological and molecular characteristics of the tumour which drives carcinogenesis6. These characteristics have informed the classification of breast cancer into five subtypes, largely based on the expression of ER and HER26 :

- Luminal A-like (**ER+/HER2-**): 40%-50% of invasive breast cancer
- Luminal B-like: ~20%-30% of invasive breast cancer
    - HER2- (**ER+/HER2-**; but ER expression lower than luminal A-like)
    - HER2+ (ER+/HER2+; but ER expression lower than luminal A-like)
- HER2-enriched (non-luminal; ER-/HER2+): 15%-20% of invasive breast cancer
- Triple negative (ER-/HER2-): ~10%-20% of invasive breast cancer

ER+/HER2- tumours comprise luminal A-like and luminal B-like HER2- tumours, which account for approximately 70% of mBC cases[7].

Except for patients with visceral crisis (imminent organ failure) in whom chemotherapy is recommended, ET, with either aromatase inhibitors (AIs) or fulvestrant, plus a CDK4/6i is the recommended standard of care (SOC) first-line (1L) treatment for patients with ER+/HER2- mBC[8].

However, approximately 20% of mBC patients progress rapidly on initial ET (i.e., have *de novo* or primary resistance, with disease progression within the first 6 months of 1L treatment with ET + CDK4/6i), while the remaining patients acquire resistance over time (secondary resistance, with disease progression at least 6 months after initiating ET for mBC)8. Several molecular mechanisms have been identified which underlie acquired endocrine resistance, including acquired variants in specific genes (e.g., *ESR1*, the gene that encodes for ERα).

Biomarker

ESR1 variants are a key mechanism of acquired resistance to ET. *ESR1* variants are somatic variants that alter the ligand-binding domain (LBD) of estrogen receptors, resulting in a ligand-independent, constitutively active conformation that enhances cancer growth, metastasis, and

[5] Cancer Australia. (2023). *Breast cancer in Australia statistics*. https://www.canceraustralia.gov.au/cancer-types/breast-cancer/statistics

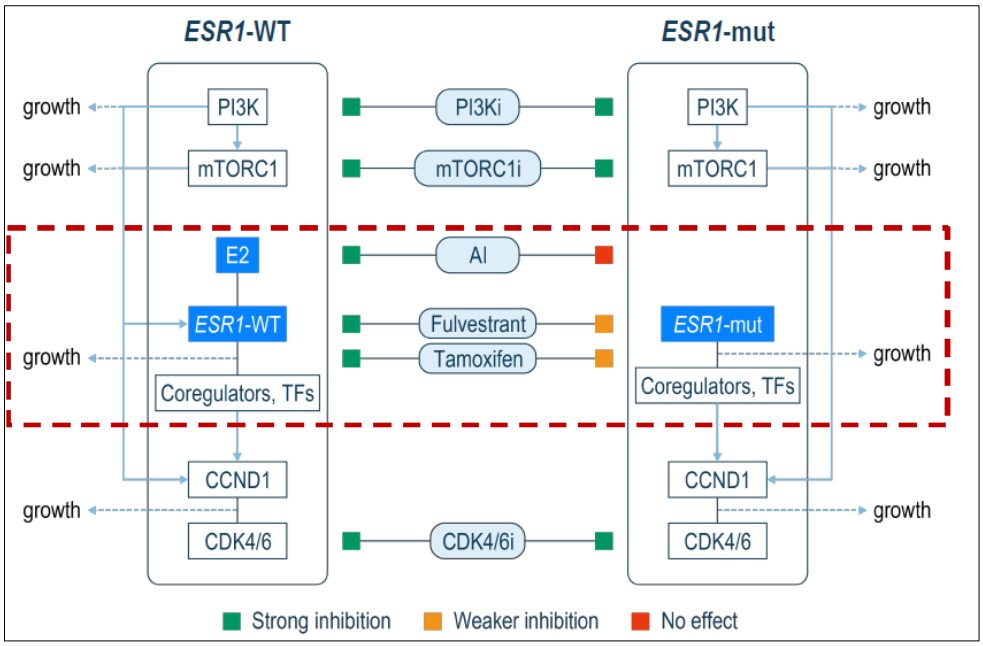
[6] Harbeck, N., Penault-Llorca, F., Cortes, J., et al. (2019). Breast cancer. *Nature Reviews Disease Primers*, *5*(1), 1–31. https://doi.org/10.1038/s41572-019-0111-2

[7] Howlader, N., Altekruse, S. F., Li, C. I., Chen, V. W., Clarke, C. A., & et al. (2014). US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*, 106(5):dju055.

[8] Gennari, A., André, F., Barrios, C. H., et al. (2021). ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Annals of Oncology*, *32*(12), 1475–1495. https://doi.org/10.1016/j.annonc.2021.09.019.

resistance. This decreases the affinity of estrogen receptors for estrogen (thereby making AIs, which reduce estrogen production, ineffective), selective estrogen receptor modulators (SERMs; e.g., tamoxifen) and selective estrogen receptor degraders (SERDs; e.g., fulvestrant) (see Figure 1).

Figure 1: Mechanisms of resistance in ER+/HER2- mBC



Source: Figure 1.3, p26 of the submission.
AI = aromatase inhibitor; CCND1 = cyclin D1; CDK4/6 = cyclin-dependent kinase 4 and 6; ER+/ HR2-mBC = estrogen receptor positive, human epidermal growth factor receptor 2 metastatic breast cancer; *ESR1-WT* = estrogen receptor 1 wild type; *ESR1*-mut = estrogen receptor 1 variant; E2 = estradiol; mTORC1(i) = mammalian target of rapamycin complex 1 (inhibitor); PI3K(i) = phosphoinositol three kinase (inhibitor); TFs = transcription factors;
Note: In the *ESR1*-WT situation, AI depletion of estrogen inhibits *ESR1* activity, SERMs such as tamoxifen alter *ESR1* binding partners and transactivation ability, and SERDs such as fulvestrant inhibit *ESR1* activity and proteolytic stability. In the *ESR1*-mut situation, AI is ineffective since *ESR1*-mut does not require estrogen, and tamoxifen and fulvestrant bind less strongly to *ESR1*-mut. CDK4/6i is effective in both *ESR1*-wt and *ESR1*-mut BC.

ESR1 variants are rarely detected in treatment-naive primary tumours[9], occurring more frequently with longer exposure to conventional ET (AIs, fulvestrant) for mBC[10]. The duration of exposure to ET in 1L treatment has increased due to combination with CDK4/6i, with median progression-free survival (PFS) ranging from 9.5 months to 28.1 months[11]. As such, *ESR1* variants predominantly emerge during 1L treatment, although they may develop during any subsequent line of therapy; therefore, testing for *ESR1* variants is relevant at each episode of disease progression[12].

[9] Hartkopf, A. D., Grischke, E., & Brucker, S. Y. (2020). Endocrine-Resistant Breast Cancer: Mechanisms and Treatment. *Breast Care (Basel)*, 15(4):347-354.
[10] 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 Res*, 23(1):85.
[11] Piezzo, M. C. (2020). Progression-Free Survival and Overall Survival of CDK 4/6 Inhibitors Plus Endocrine Therapy in Metastatic Breast Cancer: A Systematic Review and Meta-Analysis. . *International Journal of Molecular Science*, 21(17) 6400.
[12] Hartkopf, A. D., Grischke, E., & Brucker, S. Y. (2020). Endocrine-Resistant Breast Cancer: Mechanisms and Treatment. *Breast Care (Basel)*, 15(4):347-354.

Patients harbouring *ESR1* variants have a poorer prognosis, with inferior PFS and overall survival (OS) outcomes[13], as currently available 2L+ treatments are less effective (tamoxifen, fulvestrant) or not effective (in the case of AIs). Chemotherapy is an alternative treatment option for these patients but is associated with toxicities that impact HRQoL.

Prevalence of biomarker

It is estimated that up to 40-50% of patients with ER+/HER2- mBC will develop *ESR1* variants during their treatment course, the majority of which will arise following disease progression on 1L therapy[14].

Elacestrant treatment

While the presence of *ESR1* variants can be prognostic in that patients with these variants have poorer outcomes, they are also a likely predictive biomarker for the benefit of treatment with elacestrant, based on results from the key clinical trial, EMERALD.

Elacestrant is a potent, selective and orally active estrogen receptor-α (ERα) antagonist and degrader (SERD). Elacestrant inhibits the estrogen-dependent and independent growth of ERα-positive breast cancer cells, including those harbouring *ESR1* gene variants, thus providing a promising second line plus (2L+) treatment option for patients with ER+/HER2-mBC and *ESR1* variants. As it is administered orally, it also reduces healthcare resource utilisation costs associated with the toxicities and administration of other treatments (fulvestrant [monthly intramuscular (IM) injections] and chemotherapy) and minimises disruptions to patients' lives while maintaining their HRQoL.

Australian clinical practice is informed by international guidelines, including European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines. Both clinical guidelines have recently been updated and have added elacestrant as a recommended treatment option for postmenopausal females and adult males with ER+/HER2- mBC who test positive for *ESR1* variants after disease progression following at least one line of ET including a CDK4/6i[15,16].

Testing population

The proposed test population is men and postmenopausal women with ER+/HER2- locally advanced or mBC, who have disease progression following at least one line of ET, including a CDK4/6i. Testing is relevant at each episode of disease progression during the metastatic treatment course.

Patients who test positive for an *ESR1* variant would then be eligible for treatment with PBS-listed elacestrant.

Redacted noted that the definition, 'Any *ESR1* mutation between codons 310 and 547' was utilised to identify a patient in the EMERALD trial as '*ESR1* mutation positive' (that is, with an

[13] Turner, N. C., Swift, C., Kilburn, L., Fribbens, C., Beaney, M., & et al. (2020). *ESR1* Mutations and Overall Survival on Fulvestrant versus Exemestane in Advanced Hormone Receptor-Positive Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT Trials. Clin Cancer Res, 26(19):5172-5177.

[14] Hartkopf, A. D., Grischke, E., & Brucker, S. Y. (2020). Endocrine-Resistant Breast Cancer: Mechanisms and Treatment. *Breast Care (Basel)*, 15(4):347-354.

[15] ESMO. (2024). *ESMO Guidelines Breast Cancer Version 4. 2024.* ESMO. Retrieved Sep 08, 2024, from https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer.

[16] NCCN. (2024). *NCCN Guidelines Breast Cancer Version 4. 2024.* NCCN. Retrieved Sep 08, 2024, from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

ESR1 variant), based on the rationale that any *ESR1* mutation in the ligand domain leads to resistance to endocrine therapy.

There is no commonly agreed definition of *ESR1* variant test positivity. In the EMERALD trial, a minor allele frequency of ≥ 0.001% was employed as cutoff for detection of *ESR1* variants below which patients were defined as 'mutation not detected'. Redacted[17].

The commentary considered that the population targeted for testing in the submission was well described and was appropriate as it aligns with the trial population from EMERALD and current clinical management guidelines.

8. Comparator

Test

The proposed test comparator was no testing for *ESR1* variants. The commentary considered that this was appropriate; in the absence of testing for *ESR1* variants (and subsequent treatment with elacestrant if *ESR1* variants are detected), patients will continue with current SOC 2L+ treatments.

Drug

The proposed drug comparator was standard of care endocrine monotherapy (SOC ET). This consisted of fulvestrant (500 mg intramuscular [IM] days 1 and 15 [cycle 1], then day 1 in subsequent cycles [frequency: 28 days]), or an AI (anastrozole 1 mg per oral [po] daily, letrozole 2.5 mg po daily, or exemestane 25 mg po daily) until disease progression or unacceptable toxicity. The commentary considered that although the proposed comparator was broadly appropriate, it does not reflect the true extent of current therapies received by Australian patients.

9. Summary of public consultation input

Consultation input was received from 2 medical, health, or other (non-consumer) organisation and 4 consumer organisations.

The organisations that submitted input were:

- Rare Cancers Australia (RCA)
- Australian Genomics
- Cancer Australia
- So Brave – Australia's Young Women's Breast Cancer Charity (So Brave)
- Breast Cancer Network Australia (BCNA)
- Medical Oncology Group of Australia (MOGA) Breast Cancer Special Interest Group

Level of support for public funding

All organisations expressed support at the public funding of this application.

[17] Information will be unredacted in full when the TGA Australian Public Assessment Report (AusPAR) is available.

Comments on PICO

- So Brave noted that broad gene panels should apply not just to this subset of breast cancer patients but to all existing and future treatment protocols to reduce the impact of this investigation on the patient, improve efficiencies of testing processes with pathology, and ensure patients access the right treatment at the right time for their specific cancer. These sentiments were reflected by other organisations in their submissions.
- Australian Genomics noted the underrepresentation of Indigenous Peoples in clinical trials across various health systems, and noted it is crucial to address this issue as genetic variations can have an influence on drug response.
- Australian Genomics made specific comments addressing the outcomes as set out in the PICO, including the: incorporation of *ESR1* as a biomarker into cancer care treatment guidelines; adoption of service in other countries; and approval of a proposed NGS-based assay in other countries.
- Australian Genomics also suggested providing clarity around the number of times the service can be accessed.

Perceived Advantages

Advantages of the service noted by organisations included:

- Emotional and financial relief.
- Facilitate more personalised and effective treatment options, improving overall quality of life.

Liquid biopsies are easier to collect and transport compared to tissue specimens, potentially improving equitable access for rural and remote patients.

Perceived Disadvantages

So Brave noted that while the proposed genetic liquid biopsy assay offers significant advantages, there are some potential challenges to consider, including:

- Equitable access to this technology must be ensured, as disparities in healthcare availability could mean that some patients, particularly those in rural or lower-income areas, may struggle to access timely testing. This concern was included in other submissions by organisations.
- If the genetic liquid biopsy assay shows the benefit of a particular treatment that is not funded by the PBS, inequities of access could negate these benefits. Its effectiveness ultimately depends on the availability and reimbursement of targeted therapies—meaning that without simultaneous access to appropriate treatments, the full benefits of the test may not be realized.

Support for Implementation /issues

- So Brave noted that successive applications for therapies targeting specific mutations cannot and should not be assessed or implemented in isolation—what is required is a comprehensive, full-panel genomic assay to identify all actionable mutations in a patient's cancer. A targeted assay of liquid biopsy represents a crucial step toward achieving this, but without a standardised, broad-spectrum genomic testing approach, patients risk missing out on life-saving treatment.

- Australian Genomics stated that in the absence of public funding for *ESR1* mutation testing or treatment, patients must pay for the test and associated treatment out-of-pocket, which is not a feasible strategy in the long-term and does not align with equity of access of healthcare services and treatments for all Australians.
- The MOGA Breast Cancer Special Interest Group stated that, because there are multiple actionable variants in the proposed population, a panel screen or full profiling may be more efficient than a single gene test, to determine eligibility for multiple different drugs at the same time using a single biopsy sample.
- Australian Genomics noted the following points of consideration for implementation:
    - Equity of access issues relating to access to specialist medical oncology and interventionalist radiologists required to aid in specimen request and test request.
    - Issues regarding access to the likely private pathology services that would perform the test.
    - A lack of prospective studies which consider the effect of including ESR1 mutation status in clinical patient management.

10. Characteristics of the evidence base

The approach taken in the submission is to present:

- Direct evidence of the effect of targeting *ESR1* missense variants using ctDNA extracted from peripheral blood plasma via NGS with elacestrant using evidence from the EMERALD trial.
    - The EMERALD trial was a single, randomised, Phase 3 clinical trial of elacestrant versus SOC (choice of AI or fulvestrant monotherapy) in patients with ER+/HER2- mBC who had disease progression following 1L or 2L treatment with a CDK4/6 inhibitor and ET. Random assignment was stratified according to *ESR1* variant status. The trial therefore consisted of patients who displayed the *ESR1* variant and those with *ESR1* variant not detected, and both populations were randomised to receive elacestrant or SOC. Comparative efficacy between treatment arms was analysed in the whole trial population and in patients with a detectable *ESR1* variant, using the Guardant360® CDx NGS test method (only available in the United States).
- Linked and supplementary evidence to demonstrate the:
    - accuracy and performance of the Guardant360® CDx test (clinical utility standard).
    - comparison of tissue and liquid biopsy test methods for detecting *ESR1* variants.
    - comparison of detection of *ESR1* ctDNA using NGS versus PCR.
    - concordance between different tests for detection of the *ESR1* variants.

The summary of trials/studies informing the evidence base in the submission are presented in Table 5.

Table 5: Summary of the evidence base used in the submission

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base	Used in modelled evaluation
Direct evidence: Prospective biomarker stratified randomised controlled trial of drug[a] EMERALD trial provided direct evidence reporting PFS and OS outcomes of patients who received elacestrant or SOC in patients with and without the *ESR1*-mut.				
Prognostic evidence	Given the availability of direct evidence (EMERALD), this was the focus of the evaluation. The submission identified 7 other papers as potentially relevant, of which 2 were presented (Zhang et al 2018; Zhao et al 2023).	☒ k=1 n=478	Low	Yes (*ESR1* variant population only)[C]
Health outcomes (clinical utility)	Based on direct evidence (EMERALD).	☒ k=1 n=478	Low	Yes (*ESR1* variant population only)[C]
Predictive effect (treatment effect variation)	Given the availability of direct evidence (EMERALD), this was the focus of the evaluation. The submission identified 8 other studies as potentially relevant but did not present them in any detail	☒ k=1 n=478	Low	Yes (*ESR1* variant population only)[C]
Change in patient management	No additional information was provided to describe this. The submission stated that the information relating to change in clinical management from testing, proportions of patients changing treatment plan and the number estimated to be tested at each line of therapy & diagnostic yield and number needed to test have been presented in Section 1 and 4 of the submission. Assumed by the evaluation to be also implicitly addressed by the EMERALD trial if the test and the drug were available in Australia.	☐ k=0 n=0	-	Not used
Linked evidence				
Accuracy and performance of the Guardant360® CDx test	FDA's Summary of Safety and Effectiveness (January 2023) Guardant360® CDx Technical Information document EMERALD trial These sources were used to demonstrate the analytical performance, precision and concordance of the clinical utility standard. The submission identified numerous other studies relating to Guardant360® CDx assays but were not considered during the evaluation as they were poster abstract or not relevant to the submission's clinical claim.	☒ k=3 n=756 (24+254+478)	- - -	Not used
Others				
Comparison of tissue and liquid biopsy test methods for detecting *ESR1*-mut	Two meta-analyses (Najim et al, (2023) and Raei et al, (2024)). The submission appeared to have presented 16 studies (as many were repeated across the submission). 13 of the studies may offer data for concordance of studies of tissue and liquid biopsy test methods for detecting *ESR1*-variant but were not	☒ k=2 n=3,133	Moderate[b]	Not used

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base	Used in modelled evaluation
	presented in a manner that permitted comparison across each of the methods for the key characteristics, or outcomes sensitivity, specificity, PPV, NPV.			
Comparison of detection of *ESR1* ctDNA using NGS versus PCR	Two meta-analyses (Najim et al, (2023) and Raei et al, (2024)) were considered the strongest evidence in support of NGS versus PCR comparison. The submission identified 4 other studies that have not been described in detail.	☒ k=2 n=2,744 (1684+1060)	Moderate [b]	Not used
Concordance data	Two out of the nine studies identified by the submission were considered relevant but provided limited information to support the comparison of test performance as they were not specific to *ESR1* .	☐ k=0 n=0	-	Not used

Source: Compiled during the evaluation from section 2B.3.1. Study design, pp171-173 of the submission.
ESR1 = estrogen receptor 1; NPV = negative predictive value; OS = overall survival; PFS = progression-free survival; PPV = positive predictive value; SOC = standard of care.
[a] Population with and without the biomarker randomised to drug or usual care, stratified according to *ESR1* variant status.
[b] Reasons for moderate rating include lack of defined PICO, inclusion of non-randomised studies without rationale, study inclusion done by single author, data extraction done by single author, no funnel plot for publication bias.
[C] The *ESR1* positive subgroup of patients from the EMERALD trial, with 6 patients who received CDK4/6i in the adjuvant setting removed from analysis (n=222).
k=number of studies; n=overall number of patients

11. Comparative safety

Adverse events from testing

The submission claimed that there are no adverse events associated with testing for *ESR1* variants compared to a no testing strategy. The commentary considered that this was reasonable as the test involves a liquid biopsy which is low risk and minimally invasive.

Adverse events from changes in management

In the key clinical trial, EMERALD, patients in the elacestrant arm had a greater risk of experiencing treatment emergent adverse events (TEAEs) related to trial therapy (63.3% vs 43.5%), Grade ≥3 TEAEs (27.0% vs 20.9%) and TEAEs leading to interruption (15.2% vs 5.2%) compared to SOC. There were 3 patients with serious TEAEs related to treatment with elacestrant (2 patients had nausea, and 1 had vomiting, cholecystitis acute, decreased appetite, dehydration, and pulmonary embolism).

The most common Grade ≥3 TEAEs observed in the elacestrant arm were gastrointestinal (nausea) and musculoskeletal and connective tissue (back and bone pain) disorders. There were no deaths considered study drug related.

A false positive result of *ESR1* variant would lead to inappropriate treatment with the targeted therapy, elacestrant. The submission noted that the clinical impact of treating patients with a potential false positive *ESR1* result was captured in the clinical effectiveness results, as patients with and without *ESR1* were treated with elacestrant. This was not considered reasonable as targeted treatment would only be appropriate for patients with the *ESR1* variant.

In clinical practice, a false negative result of an *ESR1* variant would lead to inappropriate treatment with SOC, with patients likely to achieve worse outcomes than if they were correctly treated with elacestrant (based on the results from the EMERALD trial).

The submission did not report false positives or false negatives in the EMERALD trial or describe how the potential for these results were managed.

12. Comparative effectiveness

Effectiveness (based on direct evidence)

The EMERALD trial was the main evidence base for prognostic, health outcomes and predictive effect. Details of the EMERALD trial are provided in Table 6 and Table 7 below.

Table 6: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
EMERALD (NCT03778931)	**Clinical study reports:** • Elacestrant Monotherapy vs Standard of Care for the Treatment of Patients with ER+/HER2- Advanced Breast Cancer Following CDK4/6 Inhibitor Therapy: A Phase 3 Randomised, Open-Label, Active-Controlled, Multicenter Trial.	RAD1901-308
	• Elacestrant Monotherapy Vs. Standard Of Care For The Treatment Of Patients With ER+/HER2- Advanced Breast Cancer Following CDK4/6 Inhibitor Therapy: A Phase 3 Randomised, Open-Label, Active-Controlled, Multicenter Trial (EMERALD). Overall Survival Addendum As Of 02 September 2022	RAD1901-308
	• Phase 3 Trial of Elacestrant vs. Standard of Care for the Treatment of Patients With ER+/HER2- Advanced Breast Cancer https://clinicaltrials.gov/study/NCT03778931	NCT03778931
	Key study publications: • Bidard, FC. et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial	J Clin Oncol. 2022 Oct 1;40(28):3246-3256.
	Additional publications: • Anonymous Erratum: Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial	J Clin Oncol. 2023 Aug 10;41(23):3962
	• Bardia, A. et al. Elacestrant in ER+, HER2− Metastatic Breast Cancer with *ESR1*-Mutated Tumours: Subgroup Analyses from the Phase III EMERALD Trial by Prior Duration of Endocrine Therapy plus CDK4/6 Inhibitor and in Clinical Subgroups	Clin Cancer Res 2024 OF1–OF11

Source: Table 2.55, pp168-169 of the submission

CDK4/6 = cyclin-dependent kinase 4/6; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; ER+ = oestrogen receptor positive; HER2- = human epidermal growth factor receptor 2 negative.

Table 7: Key features of the included evidence

Trial	N	Design/ duration	Patient population	Outcome(s)	Use in modelled evaluation
Elacestrant vs SOC (in both *ESR1* variant positive and negative patients)					
Bidard 2022	478	R, DB, MC median duration follow-up 15.9 months for PFS (26.0 months for OS)	ER+/HER2- mBC with disease progression following at least one line of ET, including a CDK4/6i	PFS, OS, ORR, DoR, CBR	PFS, OS, TTD, TCD

Source: Compiled during the evaluation using information from Section 2B.4 of the submission.
CBR = clinical benefit rate; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; DB=double blind; DoR = duration of response; ER+/HER2- mBC = oestrogen receptor positive/ human epidermal growth factor receptor 2 negative metastatic breast cancer; *ESR1* = estrogen receptor 1; ET = endocrine therapy; MC=multi-centre; OS = overall survival; ORR = objective response rate; PFS=progression-free survival; R=randomised; SOC = standard of care; TCD = time to chemotherapy or death; TTD = time to treatment discontinuation

Both primary endpoints of the study (PFS in all subjects (whole trial population) and in *ESR1* variant subjects) were met by the September 2021 data cutoff date (median follow up 16 months).

In the whole trial population, elacestrant demonstrated statistically significant improvements in PFS, reducing the risk of disease progression or death by 30% compared to SOC (hazard ratio [HR] 0.70, 95% confidence interval [CI]: 0.55 to 0.88). The median PFS was 2.79 months for the elacestrant group and 1.91 months for the SOC group.

In patients with *ESR1* variant tumours, elacestrant was associated with statistically significant improvements in PFS, reducing the risk of disease progression or death by 45% compared to SOC (HR 0.55 [95% CI: 0.39 to 0.77]). The median PFS was 3.78 months for the elacestrant group compared to 1.87 months in the SOC group.

An updated analysis for the key secondary outcome of OS was performed with a cut-off date of 2 September 2022, by which time 50% of events had occurred (median follow-up 26 months). The difference in OS between the elacestrant and SOC treatment arms was not statistically significant for either the whole trial population or the *ESR1* variant population.

On the basis of the benefits and harms reported in the evidence base, the submission claimed that relative to no testing and SOC, genetic testing for *ESR1* variants and treatment with elacestrant has superior effectiveness and a different and manageable safety profile.

The commentary considered that the claim for superior effectiveness for elacestrant compared with fulvestrant or AI monotherapy was supported based on PFS results reported from the EMERALD trial. However, the SOC in the EMERALD trial may not be fully representative of the true extent of current therapies received by Australian patients, thus the applicability of the treatment effect observed in the EMERALD trial in Australian clinical practice is uncertain and the level of benefit may be overestimated due to possibly improved SOC 2L+ treatment outcomes in Australian practice compared to the EMERALD trial. Additionally, there were no statistically significant differences between treatment arms for other secondary outcomes, including OS, objective response rate (ORR), duration of response (DoR) or health related quality of life (HRQoL).

Patients in the elacestrant arm in EMERALD had a greater risk of experiencing TEAEs related to trial therapy (63.3% vs 43.5%), Grade ≥3 TEAEs (27.0% vs 20.9%) and TEAEs leading to treatment interruption (15.2% vs 5.2%). The commentary considered that an inferior safety claim would be more appropriate, although noted that the adverse events are likely manageable (the most common Grade ≥3 TEAEs observed in the elacestrant arm were gastrointestinal (nausea) and musculoskeletal and connective tissue (back and bone pain) disorders).

Prognostic evidence and predictive effect of *ESR1* variants

The submission presented results from EMERALD of the subgroup of patients without *ESR1* variants, although noting that EMERALD was not powered to demonstrate benefit in this population. A comparison of the PFS and OS outcomes between the whole trial population and patients with and without a detectable *ESR1* variant is presented in Table 8 below.

Table 8: Results of PFS and OS in EMERALD comparing whole of trial population and those with and without ESR1 variant subgroup population (BIRC, ITT)

Population	Elacestrant		SOC [c]		HR (95% CI); p-value
	Event n/N (%)	Median, months (95%CI)	Event n/N (%)	Median, months (95%CI)	
PFS[a]					
Whole trial population	144/239 (60.3)	2.79 (1.94, 3.78)	156/239 (65.3)	1.91 (1.87, 2.10)	**0.70 (0.55, 0.88); 0.0018**
ESR1-mut	62/115 (53.9)	3.78 (2.17, 7.26)	78/113 (69.0)	1.87 (1.87, 2.14)	**0.55 (0.39, 0.77); 0.0005**
ESR1-mut-nd	82/124 (66.1)	1.94 (1.87, 3.55)	78/126 (61.9)	1.97 (1.87, 2.20)	0.86 (0.63, 1.19); 0.31
				Test for interaction [d]	*0.06*
OS[b]					
Whole trial population	124/239 (51.9)	24.61 (20.67, 29.47)	121/239 (50.6)	22.57 (18.14, 28.88)	0.91 (0.71, 1.18); 0.48
ESR1-mut	61/115 (53.0)	24.18 (20.53, 28.71)	60/113 (53.1)	23.49 (15.64, 29.90)	0.90 (0.623, 1.30); 0.58
ESR1-mut-nd	63/124 (50.8)	26.12 (18.83- NC)	61/126 (48.4)	22.57 (18.37, 30.98)	0.92 (0.65, 1.31); 0.65
				Test for interaction [d]	*0.93*

Source: Table 2.5: Number of patients with reference to *ESR1*-mut status (ITT), p75 of the submission
CI = confidence interval; *ESR1* = estrogen receptor 1; *ESR1*-mut = *ESR1* variant; *ESR1*-mut-nd = *ESR1* variant not detected; HR = hazard ratio; ITT = intent to treat analysis population; NC = not calculable; OS = overall survival; PFS = progression-free survival; SOC = standard of care.
[a] September 2021 data cut off
[b] September 2022 data cut off
[c] SOC in the EMERALD trial comprises of choice of aromatase inhibitor (AI) or fulvestrant monotherapy which may not reflect the true extent of current therapies received by Australian patients.
[d] *Test for interaction conducted during the evaluation comparing the two ESR1 variant subgroups*. p value < 0.05 suggesting that presence of *ESR1* variant was a potentially significant treatment effect modifier
Note: p-values using stratified log-rank test.
Bold text indicates a statistically significant p-value

In the non-*ESR1* variant subgroup, there was no statistically significant difference in PFS between elacestrant and SOC.

Analysis of PFS outcomes for patients treated with SOC indicated that those with *ESR1* variants had slightly poorer median PFS compared to patients without *ESR1* variants (1.87 months vs 1.97 months) (see Table 8). This appears to suggest that patients with *ESR1* variants have poorer PFS prognosis than patients without *ESR1* variants (although noted this difference was small and 95% CIs overlapped between groups). However, patients with *ESR1* variants had greater median OS compared to patients without *ESR1* variants in the SOC arm (23.49 vs 22.57 months). The submission did not present a test for interaction between these subgroups to support and quantify the association between the treatment effect and the covariate defining the subgroup. The test for interaction between the *ESR1* and non-*ESR1* variant subgroups conducted during the evaluation did not suggest significant *ESR1* variant treatment effect modification (p=0.055), although noting the limitations of the analysis (based on point estimates and not adjusted for multiplicity). The commentary suggested replicating this analysis with patient-level

data from the EMERALD trial. The PSCR (p9) noted that the test for interaction from Bidard 2022, which utilised patient level data, gave a p-value for interaction of 0.053.

The commentary considered the evidence to demonstrate the predictive value of *ESR1* biomarker for the treatment with elacestrant uncertain. The ESCs noted that no test for interaction reached statistical significance but noted that there appeared to be minimal benefit in the non-*ESR1* subgroup and the clinical rationale and mechanism of action for elacestrant supported the claim that *ESR1* is likely to be a predictive biomarker for treatment with elacestrant. The ESCs considered the claim of codependence to be reasonable overall, but the extent of treatment effect variation to be uncertain.

Change in management in practice

The EMERALD trial offered a rationale for change in management of patients based on their *ESR1* status. Studies of changes in management such as referrals, re-testing, prescribing rates or other clinical management decisions were not available, which was considered consistent with the lack of *ESR1* testing in Australia.

Linked evidence

In the key clinical trial, EMERALD, *ESR1* variant status was evaluated in ctDNA extracted from blood (liquid biopsy) using the Guardant360® CDx test. Therefore, this test is the clinical utility standard. The Guardant360® CDx test is not available in Australia.

Precision (reliability) for detection of ESR1 variants

The Guardant360® CDx Technical Information for the United States contains details of precision and diagnostic accuracy for detection individual *ESR1* variants (Guardant Health, Inc., 2023).

Precision (reliability) for detection of *ESR1* variants was analysed for *ESR1 H356D, E380Q, G442A, S463P, Y537S*, and *D538G* variants[18] at 5 ng cell free DNA (cfDNA) input using breast cancer patient samples (Table 9).

Table 9: Summary of Guardant 360 precision results for detection of ESR1 variants

***ESR1* Missense variants**[a]	**Observed MAF%**	**Relative LoD Level**[b]	**Number Positive/ Number Expected**	**PPA (95% CI)**
E380Q	1.0	1.0x	24/24	100% (85.8, 100)
Y537S	1.0	1.0x	23/24	95.8% (78.9, 99.9)
D538G	1.1	1.0x	23/24	95.8% (78.9, 99.9)
H356D	2.1[c]	2.0x	20/24	83.3% (62.6, 95.3)
H356D	3.1[c]	2.9x	22/24	91.7% (73.0, 99.0)
G442A	2.3	2.1x	24/24	100% (85.8, 100)
S463P	2.8	2.6x	24/24	100% (85.8, 100)

Source: Table 2.21: Summary of Precision Results for *ESR1*-Mut, p107 of the submission.

CI = confidence interval; *ESR1* = estrogen receptor 1; *ESR1*-mut = estrogen receptor 1 variant; LoD = limit of detection; MAF = mutant allele fraction; PPA = positive percent agreement.

[a] variants resulting in amino acid substitutions of: E380Q = glutamate 380 to glutamine; Y537S = tyrosine 537 to serine; D538G = aspartate 538 to glycine; H356D = histidine 356 to aspartate; G442A = glycine 442 to alanine; S463P = serine 463 to proline.

[b] Compared to the established LoD for the prevalent *ESR1* missense mutations.

[c] Note that the observed MAF is the average variant MAF from all samples with a reported variant (i.e., excluding dropouts)

[18] H356D = histidine 356 to aspartate substitution; E380Q = glutamate 380 to glutamine substitution; G442A = glycine 442 to alanine substitution; S463P = serine 463 to proline substitution; Y537S = tyrosine 537 to serine substitution; D538G = aspartate 538 to glycine substitution.

The FDA evaluator described this study as a combined limit of detection (LoD) Confirmation and Precision Study and stated further that "The LoDs for *ESR1* G442A and S463P were confirmed; however, the study result of the LoD confirmation and precision study for *ESR1*, H356D has a PPA of 83.3% or 91.7%, which did not achieve agreement of ≥ 95% across all conditions for H356D at 5 ng of cfDNA input. […] By evaluating 25 additional replicates from the same sample pool for H356D, PPA of 95.9% was achieved". The FDA document also noted that "No *ESR1* false positive mutations were detected (NPA 100%, 240/240)".

Redacted noted that not all possible *ESR1* variants were tested using the Guardant360® CDx testing method. The clinical significance of variants not encompassed by the Guardant360® CDx method is unknown.

It was understood that for the more common variants (E380Q, Y537S, D538G), at least 95% agreement with a 5 ng cfDNA sample represents assay performance achievable at the LoD. For the rare variants (H356D, G442A, S463P), at least 2 or up to 3 times the 5 ng sample was needed to achieve the PPA values reported.

The values presented show there is variability between the studied reagent lot-instrument-operator combinations, especially for detection of the H356D variant. Although false positives did not appear to be an issue, this has implications for assay sensitivity and false negative rates obtained with the Guardant360® CDx clinical utility standard, especially for rare variants (H356D, G442A and S463P).

Concordance using EMERALD samples

The detection of alterations by Guardant360® CDx was compared to results of an externally validated NGS assay and presented in Table 10.

Table 10: Summary of concordance between Guardant360 and comparator, externally validated NGS assay

	Guardant (+), Comparat. (+)	Guardant (+), Comparat. (-)	Guardant (-), Comparat. (+)	Guardant (-), Comparat. (-)	Patients (n)	PPA (95% CI)	NPA (95% CI)	PPV (95% CI)	NPV (95% CI)
ESR1 variants	121	20	3	110	254	98% (93, 99)	85% (77, 90)	86% (79, 91)	97% (93, 99)

Source: Table 2.27, p115 of the submission.
CI = confidence interval; estrogen receptor 1; NGS = next generation sequencing; NPA = negative percent agreement; NPV = negative predictive value; PPA = positive precent agreement; PPV = positive predictive value.
*The Clopper-Pearson Exact Method was used for the confidence interval analysis

Without a reference standard or comment on whether this analysis included validated true positive and true negative control samples, this concordance data provides only limited support for the analytical performance of the clinical utility standard. As the comparator method in this concordance study is unidentified and/or not available in Australia, this is not informative for the comparison with potential tests for the Australian market.

Based on the positive predictive value (PPV) and negative predictive value (NPV) presented, the Guardant360® CDx assay could be interpreted as reporting 14% false positives (based on 86% PPV) and 3% false negatives (based on 97% NPV). This is quite different from the performance and LoD values presented in the precision/LoD study above (Table 9).

The commentary considers the assumption of 100% accuracy made in Section 3 of the submission is likely to be inappropriate both in terms of the EMERALD trial data and in Australian clinical practice using another NGS method.

Comparison of detection of ESR1 ctDNA in plasma versus tumour tissue

Two meta-analyses were used to inform the concordance of *ESR1* variant detected with liquid biopsy versus tissue biopsy (Raei et al. 2024 and Najim et al. 2023).

The Najim et al, (2023) meta-analysis included 2,744 pooled tissues and plasma samples for this analysis. Plasma samples were used in 57.1% (1,568/2,744) of the study population, tissue samples in 37.7% (1,033/2,744), and tissue-plasma pairs in 5.2% (143/2,744). Incidence of *ESR1* mutation was compared between plasma versus tissue samples and between ddPCR versus NGS. Of the meta-analysed studies, nine used tissue biopsy while five used plasma samples/liquid biopsy. The authors found no significant difference in *ESR1*-mut incidence between plasma and tissue samples (P = 0.34, Figure 2A.4.2).

A meta-analysis by Raei et al. (2024) examined the diagnostic accuracy of *ESR1*-mut detection in cfDNA samples of breast cancer patients. The study included 13 studies with 15 cohorts with a sample size ranging from 6 to 77, including 389 participants.

Compared to histopathological examination of tissue, cfDNA assessment could be tested with a sensitivity of 75.52% (95% CI 60.19 – 90.85). Significant heterogeneity was observed (I^2 = 75.47%, p<0.001). Similarly, the meta-analysis value for specificity of *ESR1*-mut detection was 88.20% (95% CI 80.99 – 95.40), also with high heterogeneity (I^2 = 81.36%, p<0.001).

The meta-analysis demonstrated a PPV of 56.94% (95% CI 41.70 – 72.18) and a NPV of 88.53% (95% CI 82.61–94.44) for *ESR1* detection by cfDNA. The heterogeneity was moderate for NPV (I^2 = 43.36%, P > 0.05) but notable heterogeneity was observed for PPV (I^2 = 73.36%, p<0.001). Forest plots are shown for PPV and NPV. The meta-analysis value of test accuracy was 88.96% (95% CI 83.23 – 94.69), derived by examining sensitivity and specificity. Significant heterogeneity was observed (I^2 = 78.91%, p<0.001).

Comparison of detection of ESR1 in ctDNA using NGS versus PCR

The submission stated that testing using PCR methods such as ddPCR or qPCR were not considered appropriate for testing *ESR1* variant for the following reasons:

- ddPCR would offer a limited read of the *ESR1* variant and may not be optimal to detect all variants **redacted** without performing two or more consecutive tests. Also, ddPCR needs much more technical setup than NGS which is a ready to use solution.
- qPCR is not considered optimal for detecting *ESR1* variant in ctDNA from blood samples for several reasons (low MAF, low range of mutation detection; qPCR might show cross-reactivity with similar sequences, leading to false positives; recommendations in clinical guidelines to use NGS). This submission also stated that qPCR has never been investigated in a clinical trial for the detection of *ESR1* variant.

As such, testing using PCR methods such as ddPCR or qPCR were not presented in the submission.

The commentary considered this inappropriate as it does not align with the key assessment questions agreed by PASC at the August 2024 PASC meeting which includes the need to demonstrate the difference between NGS, ddPCR and qPCR methodologies and implications of discordance between methods (p12, Ratified PICO confirmation, August 2024 PASC meeting).

The two meta-analyses by Najim et al, (2023) and Raei et al, (2024) included studies which compared these methodologies and are therefore considered in the commentary.

The Najim et al, (2023) meta-analysis included studies using ddPCR (k=7, n=1,684) and NGS (k=9, n=1,060) to determine *ESR1*-mut in tissue and plasma samples. The incidence rates of

ESR1-mut using ddPCR and NGS were 26% (95% CI, 20 – 33%) and 19% (95% CI, 13 – 27%), respectively. Forest plots are shown in Figure 2A.4.6. The authors found no significant difference in *ESR1*-mut incidence between ddPCR and NGS techniques (P= 0.15).

In the Raei et al. (2024) meta-analysis, comparisons between digital[19] PCR or NGS assays were presented as a subgroup analysis. Specificity of NGS and digital PCR was comparable (90.14%; range 79.17 – 101.10 versus 90.44%; range 82.55 – 98.33, respectively) but sensitivity for NGS (56.78%, range 13.89 – 99.67) was lower than for digital PCR (81.01%; range 64.04 – 97.99).

Non-comparative concordance data from ESR1 assays in Australia

The submission provided a list of assays available in Australia that could potentially be used to detect *ESR1* variants in liquid biopsy samples (Table 1). These include Thermofisher Oncomine cfDNA Breast, Thermofisher Oncomine Precision GX tests, Roche Avenio ctDNA expanded v2 and Illumina TruSight 500 Oncology ctDNA. None of the ctDNA tests for *ESR1* variants are TGA-registered.

The submission presented analytical data for assays described as approved and available in Australia and which could be used to detect *ESR1* variants in plasma samples, compared to the clinical utility standard (Guardant360® CDx). Limit of detection (LoD), sensitivity and specificity were extracted from the respective manufacturers information and represent overall analytical performance data.

The commentary noted that no comparative evidence of concordance between the clinical utility standard (Guardant360® CDx) and *ESR1* assays available in Australia was presented.

The commentary considers this evidence is important given the redacted

Summary of linked evidence of test performance

The commentary considered that significant gaps remain regarding performance of the clinical utility standard, the Guardant360. Furthermore, evidence presented in the submission for test performance data to support the comparison between the clinical utility standard used in the EMERALD trial and the tests that might be used in Australia was extremely limited.

The following key concerns remain:

- The comparisons of concordance data for the Guardant360 assay and the corresponding NGS assays that may be available in Australia (in particular the Oncomine Precision assay) presented in the submission was of limited value to draw valid conclusions.
- CDxGuardant360 is not available in Australia and the lack of TGA-approved testing approaches remains an issue. The submission has not presented sufficient evidence to demonstrate that testing in clinical practice would be adequately comparable to that used in the EMERALD trial, which is a key requirement for the safe and effective use of elacestrant for treatment in patients with *ESR1* variants.
- Based on the information provided in the submission, it remains unclear whether there is sufficient capacity in current Australian laboratories to meet testing requirements for *ESR1* variants in ctDNA.

[19] In this case, digital PCR covers both droplet (ddPCR) and chip-based techniques, though the majority of studies included in the Raei et al, (2024) paper were of the droplet method.

- **Redacted.** Evidence supplied during the evaluation in the **redacted** indicated that testing is being established in two laboratories. Assessment of *ESR1* testing in those labs will require more details of test performance than was provided in the **redacted**.

Claim of codependence

- The submission claimed that, based on results from the EMERALD trial, using *ESR1* variant status as a predictive biomarker for treatment with elacestrant optimises treatment outcomes and informs physicians about the likelihood of clinical benefit in patients with ER+/HER2- mBC who have disease progression following at least one line of ET, including a CDK4/6 inhibitor.
- In the analysis of non-*ESR1* variant patients in EMERALD, there was no statistically significant difference in PFS between elacestrant and SOC (HR 0.863 [95% CI: 0.628 – 1.186)], p-value = 0.3082), thus suggesting that ER+/HER2- mBC patients without ESR1 variants may be unlikely to achieve additional benefits from treatment with elacestrant compared to current SOC 2L+ therapies. However, the test for interaction for the PFS outcome between the *ESR1* and non-*ESR1* variant subgroup conducted during the evaluation did not suggest that the *ESR1* variant was a significant treatment effect modifier (p=0.055), noting the limitations of the analysis (using point estimate data and not adjusting for multiplicity).
- The PSCR (p9) noted that the test for interaction from Bidard 2022, which utilised patient level data, gave a p-value for interaction of 0.053. The PSCR argued that the EMERALD trial results clearly demonstrate a difference in PFS response between the *ESR1* variant and non-variant subgroups and noted that the primary endpoint of PFS was statistically significant for both the ITT and *ESR1* variant populations.
- The ESCs noted that this test for interaction did not reach statistical significance but noted that there appeared to be minimal benefit in the non-*ESR1* subgroup and the clinical rationale and mechanism of action for elacestrant supported the claim that *ESR1* is likely to be a predictive biomarker for treatment with elacestrant. The ESCs considered the claim of codependence to be reasonable overall, but the extent of treatment effect variation to be uncertain. The ESCs also noted that **redacted**.

13. Economic evaluation

The submission presented a modelled economic evaluation, based on the direct randomised trial, EMERALD, comparing elacestrant to SOC (fulvestrant or AIs) in a population of patients with ER+/HER2-mBC who harbour an *ESR1* variant and who have disease progression following at least one line of ET, including a CDK4/6i. The type of economic evaluation presented was a cost-utility analysis. The commentary considered this was appropriate given the submission's clinical claims that elacestrant is superior in terms of effectiveness and has a different but manageable safety profile compared to SOC.

The economic model adopted a partitioned survival analysis approach using Kaplan Meier (K-M) data from the EMERALD trial outcomes of OS, PFS, and time to chemotherapy or death (TCD) until the mean OS follow-up (18 months), then extrapolated using fitted parametric curves to estimate the proportion of patients in four health states (progression-free (PF), progressed disease (PD) [on chemotherapy], PD [not on chemotherapy] and death) over a ten year time horizon. Time-to-treatment discontinuation (TTD) was extrapolated to estimate the proportion of patients who discontinued treatment with elacestrant or SOC.

A summary of the economic model structure, key inputs and rationale is presented in Table 11.

Table 11: Summary of model structure, key inputs and rationale

Component	Summary
Comparison modelled	NGS testing for *ESR1* variants available and treatment with elacestrant for patients with *ESR1* variants vs Testing not available and SOC for patients with *ESR1* variants.
Time horizon	10 years in the model base case vs 26 months follow up (median OS) for elacestrant and SOC arms respectively in the EMERALD trial
Outcomes	LYG and QALYs
Methods used to generate results	Partitioned survival analysis
Health states	Progression-free, progressed disease (divided into those receiving chemotherapy and those not receiving chemotherapy) and dead. TTD included to account for time on treatment.
Cycle length	28 days
Test parameters	Not described Prevalence: 100% (implied as population only consists of patients with *ESR1* variants). Test accuracy/performance estimates (implied) Sensitivity = 100% Specificity = 100% Test failure rate = 0% Test uptake rate = 100%
Implications of false positive and false negative results	Not described
Allocation to health states	Derived from PFS, OS, TTD and TCD K-M data from the *ESR1*-variant cohort in EMERALD (excluding 6 patients who received CDK4/6i in the adjuvant setting), then extrapolated using parametric survival analysis for remaining time horizon. Truncation point for all model outcomes was the mean OS follow up from the 2022 data cut (18 months [claimed by the submission; this could not be verified]).
Extrapolation method	Independent parametric models were fitted to each treatment arm with Log-logistic (OS), Generalised Gamma (PFS), Log-normal (TCD) and Generalised Gamma (TTD) selected in base case for elacestrant and Gompertz (OS), Generalised Gamma (PFS), Log-normal (TCD) and Generalised Gamma (TTD) selected in base case for SOC, based on goodness of fit/visual inspection/assessment of the clinical plausibility of the extrapolation. Convergence was not assumed to occur within the modelled time horizon. 50% of LYs gained, 48% of QALYs gained and 29% of costs in the elacestrant arm and 39% of LYs gained, 34% of QALYs gained and 35% of costs in the SOC arm occur in the extrapolated period.
Health related quality of life	A linear mixed-effects regression model was fitted to EQ-5D-5L data from the EMERALD trial with Australian tariffs applied. A baseline utility value, accounting for mean age of the population and proportion of patients receiving 2+ prior LOT was used for the PF state (excludes time-varying age and G3/4 AE decrements). The utility value for PD health state was derived from a PD multiplier (sourced from the Lloyd 2006) that was applied to the PF health state value from EMERALD. Utility decrements related to IM administration (from fulvestrant treatment as part of SOC) and subsequent chemotherapy treatment were derived from the literature Utility values used in model: PF=0.876 PD=0.543 Age decrement= -0.0014 Grade 3/4 AE decrement= -0.0830 IM administration = -0.0040 Chemotherapy treatment = -0.113

Source: Table 2.78, p218 and Table 3.1, p254 of the submission

AE= adverse event; EQ-5D-5L = EuroQol 5 dimension 5 level; *ESR1* = estrogen receptor 1; ICER = incremental cost-effectiveness ratio; IM = intramuscular injection; K-M = Kaplan-Meier; LOT= lines of therapy; LYs = life years; LYG = life years gained; OS = overall survival; PBAC= Pharmaceutical Benefits Advisory Committee; PD = progressed disease; PF = progression free; PFS = progression-free survival; QALY = quality-adjusted life year; SOC = standard of care; TCD = time to chemotherapy or death; TTD = time to treatment discontinuation

No test variables were incorporated in the economic model; the model input population (or starting population) consisted of the *ESR1* variant population only from the EMERALD trial. As such, the model implied that testing for *ESR1* variants in ctDNA extracted from blood plasma through NGS methodology is associated with no false negative or false positive results, test uptake is 100%, the test failure rate is 0% and no retesting occurs. The commentary considered that the implied assumptions regarding test accuracy were not appropriate or justified based on the test performance evidence presented.

The commentary noted the submission's approach for the economic model was not consistent with MSAC/PBAC guidelines which state that, for a co-dependent technology, the model structure should capture patients at the point of testing such that the incremental benefits and costs are included for those who are both positive and negative for the test (the whole trial population). The commentary also noted that the submission's approach was not consistent with advice from PASC, which considered that cost modelling for both NGS and ddPCR methodology in the detection of *ESR1* variants should be included in the assessment.

In EMERALD, 47.7% (228/478) of eligible patients tested positive for an *ESR1* variant (based on one test per patient); the submission claimed that this means that 2.10 patients must be tested to identify one *ESR1* variant positive patient.

The submission also claimed that since the prevalence of *ESR1* variants in ER+/HER2- mBC patients from the EMERALD trial reflects patients who were 2nd and 3rd line post CDK4/6i treatment, this reflects the rate of *ESR1* variants across multiple lines of ET. Therefore, the submission claimed that the economic model implicitly evaluates multiple rounds of testing, and it is not necessary to evaluate subsequent rounds of testing separately.

The expected cost of the proposed *ESR1* test is around $1,500 (based on advice from a large treating centre pathology service). The commentary noted that this is higher than similar tests currently listed on the MBS, including testing for germline gene variants *BRCA1/2* and *PALB2* (MBS item 73296) and testing for variants known to be causative of childhood hearing loss using NGS (MBS items 73440, 73444), which are priced at $1,200 (page 17, 1782 Ratified PICO Confirmation, August 2024 PASC meeting). The model applied the cost of testing 2.10 patients to each patient in the elacestrant arm; this amounts to $3,144.74 in *ESR1* testing per patient in the elacestrant arm.

The commentary considered that methods used by the submission to determine testing costs reflect a scenario where eligible patients are only tested once following disease progression after 1 or 2 prior lines of therapy. This was not consistent with the proposed MBS restriction, which allows testing at each episode of disease progression following first line treatment. As such, the commentary considered that the costs of testing applied in the model are likely underestimated.

The base case incremental cost effectiveness ratio (ICER) was $55,000 to < $75,000 per quality-adjusted life year (QALY) gained. Test costs comprised redacted% of the total incremental costs for elacestrant. The commentary noted the submission did not present any sensitivity analyses specifically relevant to MSAC consideration of testing (e.g., varying test performance, providing a 'no test' scenario, lowering test uptake from 100%, introducing a test failure possibility, or varying the biomarker prevalence). Given the structure of the model, sensitivity analyses could not be conducted during the evaluation to test the impact of these assumptions. However, it is likely that the assumptions made regarding 100% test accuracy and 0% failure rate would likely

underestimate and overestimate the ICER, respectively.). The assessment group was unable to assess any sensitivity analyses as this would require considerable changes to the economic model structure.

The ESCs also requested additional sensitivity analyses, post-ESCs, to show the impact of accounting for additional testing costs for patients who undergo re-testing following progression and different unit costs for testing. Table 12 presents the results.

Table 12: Results of economic evaluation and additional sensitivity analyses post-ESCs

	Incremental cost	Incremental QALY	ICER	% change from base case
Base case (BC)	**$Redacted**	**0.60**	**$Redacted**[1]	**-**
***ESR1* prevalence [BC: overall 70% (47.7% test positive rate at each test of 2 tests)]**				
1st test - 31.3% test positive 2nd test (for 68.7% of remaining patients) -additional 12.8% test positive 40.1% total yield	$Redacted	0.60	$Redacted[2]	+Redacted%
Testing costs (base case $1,500 per test, $3,144.74 per patient identified)				
$647.05/ test[a], $1,356.53 per patient identified	$Redacted	0.60	$Redacted[1]	–Redacted%
$1,766.75/ test[b], $3,703.98 per patient identified	$Redacted	0.60	$Redacted[1]	+Redacted%

[a] An MBS fee of $647.05 sets the 85% (out-of-hospital) benefit to $550.00. This proposed fee is based on the Australian Clinical Laboratories (ACL) commercial ctDNA test for lung cancer, colorectal cancer and melanoma. The ACL test costs $550 to patients.
[b] An MBS fee of $1,766.75 sets the 85% (out-of-hospital) benefit to $1,664.35, applying MBS benefit rounding rules and a greatest permissible gap of $102.40. This proposed fee of $1,766.75 is based on the targeted consultation feedback, which stated that the indicated costs per test **redacted** is $1,664.33.
The applicant considered that the results presented in Table 12 were *ad-hoc* analyses conducted post-ESCs specifically for the purposes of informing the MSAC consideration and that interpretation of the results and their application should be limited to seeking to understand the basis for the MSAC outcome and should not be used for any other purpose.
The redacted values correspond to the following ranges:
[1] $55,000 to <$75,000
[2] $75,000 to <$95,000

14. Financial/budgetary impacts

The submission has taken an epidemiological approach to estimating the use and financial impact of the proposed codependent technologies. A summary of the key inputs for the financial estimates is presented in Table 13.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible test population: Patients with ER+/HER2- mBC progressing from a CDK4/6i	See Table 14. Sourced from analysis of annual number of patients with ER+/HER2- mBC progressing from a CDK4/6i between 2018 and 2023 (from the PBS10%), indexed against the general population growth in Australia (1.4%) for future years (sourced from ABS data). In the first year of the proposed listing, it is expected that there will be a pool of prevalent patients that progressed from a CDK4/6i in previous years who would be eligible for elacestrant under the proposed listing ('warehoused' patients). This is achieved by doubling the number of eligible patients in the test population in Year 1	Although methods used to estimate the eligible test population in future years were reasonable, the number of 'warehoused' patients included in Year 1 is likely overestimated.
Prevalence of biomarker (*ESR1* variants)	70.2% Based on calculations using the prevalence of *ESR1* variant positive patients from the EMERALD trial (47.7%) and assumptions that 100% of patients will opt for a test post 1L progression and 90% of remaining patients will opt for a further test post 2L progression (in the same year).	The proportion of ESR1 variant positive patients in the EMERALD trial (47.7%) was based on a single test and included those who had disease progression following 1L or 2L therapy. As such, the estimated prevalence of ESR1 variants applied in the financial estimates is likely overestimated.
Uptake rate	**Redacted**% in Year 1 increasing to **redacted**% in Year 4 onwards. Based on an estimate from the submission	Estimates appear reasonable given the demonstrated superior effectiveness and likely inferior but manageable safety profile
Compliance rate	95% Based on an assumption from the submission	This was reasonable – compliance in the EMERALD trial was high (99%) with low incidence rates for treatment emergent AEs.
Mean duration of treatment	160.3 days EMERALD trial (*ESR1* positive subgroup)	This was appropriate.
Offsets for comparator	Substitution of SOC 2L+ therapies including Fulvestrant (14%), AIs (Anastrozole [10%],Exemestane [9%], Letrozole [26%]), chemotherapy (Paclitaxel [3% Public/6% Private], Doxorubicin [2% Public/3% Private], capecitabine [4%]) Everolimus (3%), Goserelin (6%), Tamoxifen (1%) Based on analysis of 2L treatments in PBS 10% sample in 2023 Dosages and treatment regimens determined by EviQ recommendations Mean duration 160.3 days (as per elacestrant treatment arm in EMERALD trial)	This is inconsistent with Section 1 and 3, where SOC consisted of fulvestrant (73%) or AI (Anastrozole, exemestane, letrozole [27%]) monotherapy only. The proportions assigned to each treatment sum to 87%; this is greater than the 79% as analysed by the PBS10% sample (which included 21% of patients who had no further treatment following disease progression after 1L therapy). Further, the mean treatment duration of elacestrant was greater than the mean treatment duration of SOC in EMERALD (117.3 days). As such, the extent of substitution of current PBS listed drugs may be overestimated.

Parameter	Value applied and source	Comment
MBS items	*ESR1* variant test cost = $1500 Estimate based on costs of similar MBS items Given the expected substitution of fulvestrant, paclitaxel and doxorubicin by PBS listing of elacestrant, the need for parenteral administrations of these drugs is expected to be reduced Parenteral administration =$123.05 MBS item 13950	Estimated test costs was reasonable. Cost offsets related to parenteral administration was appropriate. The submission incorrectly applied a 80% benefit to MBS costs- this was corrected by the evaluation (85% benefit assuming all items out of hospital and greatest permissible gap (=$102.40) applied to test costs).

Source: Table 4.3, pp349-350, Table 4.5, pp350-351, Tables 4.6 & 4.8 p351 of the submission.
1L = first line; 2L = second line; AI = aromatase inhibitor; ABS = Australian Bureau of Statistics; AEs = adverse events; CDK4/6i = cyclin dependent kinase 4/6 inhibitor; ER+/HER2-mBC = estrogen receptor 1, human epidermal growth factor 2 negative metastatic breast cancer; *ESR1* =estrogen receptor 1; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; SOC = standard of care.

To estimate the size of the eligible test population, the submission conducted an analysis of the 10% PBS sample to identify the number of patients with ER+/HER2- mBC treated with a CDK-4/6i in combination with fulvestrant or an AI that progressed onto another treatment or did not seek further PBS-listed treatment in the most recent full year of data (2023). The submission stated this would represent the number of patients that would be eligible for NGS testing for *ESR1* variants to determine eligibility for treatment with PBS-listed elacestrant. The commentary considered that this approach was appropriate.

The growth rate in the proposed patient population was then indexed against the general population growth in Australia (=1.4%, informed by Australian Bureau of Statistics (ABS) data). The submission argued this was justified because there are several treatment options currently listed on the PBS for mBC and the market is well established. The commentary considered this was reasonable.

In the first year of the proposed listing (2026), the submission stated it is expected that there will be a pool of prevalent patients that progressed from a CDK-4/6i in previous years who would be eligible for elacestrant under the proposed listing ('warehoused' patients); this was achieved by doubling the number of eligible patients in Year 1. The commentary considered that, although there will likely be a larger prevalent pool of patients in Year 1, the number of 'warehoused' patients in Year 1 was likely overestimated.

The submission assumed 100% of eligible patients will opt for testing on the first occasion (progression after 1L therapy), with a prevalence rate of 47.7% (sourced from the EMERALD trial) applied to determine the predicted number of patients who test positive for an *ESR1* variant and are then eligible for treatment with elacestrant as a 2L therapy. The submission also assumed that 90% of the remaining patients in the testing population (those that did not test positive for *ESR1* variants following progression after 1L therapy) would retest upon further disease progression (progression after 2L therapy). The submission applied the same prevalence rate (47.7%) to determine the predicted number of patients who test positive for an *ESR1* variant at the second test and are then eligible for treatment with elacestrant as a third line (3L) therapy.

The commentary noted that the prevalence rate of *ESR1* variants from the EMERALD trial (47.7%) was based on a single test and included patients who had disease progression after 1L or 2L therapies. It is estimated that approximately 40-50% of patients with ER+/HER2-mBC will acquire *ESR1* variants at some stage during their disease course, with most occurring after

progression on first- or second-line therapy[20]. It was estimated that the average time between tests for *ESR1* would be 6-8 months (after disease progression following 1L therapy); PASC considered it was appropriate to include a restriction for the limit/frequency of testing to be once every 6 months (p17, 1782 Ratified PICO Confirmation, Aug 2024 PASC meeting).

Therefore, the commentary considered that while estimating up to two tests annually per patient in the eligible testing population was appropriate, to determine the eligible treatment population (predicted number of patients testing positive for *ESR1* variants) it would have been more appropriate to apply the prevalence rate from EMERALD to the total number of eligible patients in the testing population (not at each instance of testing). The commentary noted that methods used by the submission results in an annual prevalence of *ESR1* variant patients of 70%; hence the commentary considered that the number of patients eligible for treatment with elacestrant in the financial estimates was likely overestimated.

The submission presented estimated costs of testing for *ESR1* variants to the MBS, based on an expected unit price of $1500 per test. However, the commentary noted that the total test numbers presented in the submission did not match (underestimated) those expected based on methods used to determine the eligible treatment population. Further, the submission applied an 80% benefit to costs on the basis that all items are out of hospital; this should in fact be an 85% benefit, with the greatest permissible gap (=$102.4) also applied (cost to MBS per test=$1397.60). The commentary used corrected test numbers and costs, which resulted in a total cost to the MBS for *ESR1* variant testing of $10 million to < $20 million over 6 years.

Given the expected substitution of fulvestrant, paclitaxel and doxorubicin by PBS listing of elacestrant, the need for parenteral administrations of these drugs is expected to be reduced (MBS item 13950, $123.05). Although it is possible that these treatments may be displaced to later lines of therapy (rather than replaced), the commentary considered that this was appropriate as the extent to which patients will elect for further treatment post disease progression after 2L treatment is unknown.

The corrected net financial impact to the MBS of elacestrant listing is estimated to be $0 to < $10 million in Year 1 and $0 to < $10 million in Year 6 (a total of $10 million to < $20 million over 6 years) (Table 14).

[20] Hartkopf, A. D., Grischke, E., & Brucker, S. Y. (2020). Endocrine-Resistant Breast Cancer: Mechanisms and Treatment. *Breast Care (Basel)*, 15(4):347-354.

Table 14: Estimated use and financial implications

	Year 1 2026	Year 2 2027	Year 3 2028	Year 4 2029	Year 5 2030	Year 6 2031
Estimated extent of use of NGS testing for *ESR1* variants						
Number of patients eligible for testing	Redacted[a]	Redacted	Redacted	Redacted	Redacted	Redacted
Uptake rate (1st test)	100%	100%	100%	100%	100%	100%
Predicted number of patients tested (1st test)	Redacted [a,1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Prevalence of biomarker (1st test)	47.7%	47.7%	47.7%	47.7%	47.7%	47.7%
Number of patients likely to receive a positive test result (1st test)	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Uptake rate (2nd test)	90%	90%	90%	90%	90%	90%
Predicted number of patients tested (2nd test)[b]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Prevalence of biomarker (2nd test)	47.7%	47.7%	47.7%	47.7%	47.7%	47.7%
Number of patients likely to receive a positive test result (2nd test)	Redacted[1]	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]
Total predicted number of tests	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Total number of patients likely to receive a positive test result	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Estimated financial implications of the NGS testing for *ESR1* variants to the MBS						
Cost to the MBS[c] [A]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]
Estimated financial implications for changes in use of other MBS services						
Cost to MBS[d] [B]	Redacted[4]	Redacted[4]	Redacted[4]	Redacted[4]	Redacted[4]	Redacted[4]
Net financial implications						
Net cost PBS / RPBS[e] [C]	Redacted[5]	Redacted[6]	Redacted[7]	Redacted[7]	Redacted[7]	Redacted[7]
Net cost to MBS [D=A+B}	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]
Net cost Health budget [C+D]	**Redacted[5]**	**Redacted[7]**	**Redacted[7]**	**Redacted[7]**	**Redacted[5]**	**Redacted[5]**

Source: Table 4.5, Tables 4.19,4.20 & 4.21 of the submission.

ESR1 = estrogen receptor 1; MBS = Medicare Benefits Schedule; NGS = next-generation sequencing

[a] includes warehoused patients in year 1

[b] calculated by subtracting the number of patients with a positive 1st test from the number of patients tested (1st test), then multiplied by 0.90

[c] 85% benefit and greatest permissible gap (=$102.40) applied to proposed test cost for *ESR1* variants (all out of hospital services)

[d] 85% benefit applied to MBS item 13950 (all out of hospital services)

[e] Effective prices

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] < 500

[3] $0 to < $10 million

[4] net cost saving

[5] $30 million to < $40 million

[6] $10 million to < $20 million

[7] $20 million to < $30 million

Table 15 presents the results of additional sensitivity analyses on financial estimates as requested by ESCs post-ESCs.

Table 15 Additional sensitivity analyses on net cost to MBS as requested by ESCs

	Year 1 2026	Year 2 2027	Year 3 2028	Year 4 2029	Year 5 2030	Year 6 2031	Years 1-6
Total test numbers							
ESR1 prevalence							
BC: 47.7% at each test of 2 tests (submission)	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[2]
47.7% across both tests	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[2]
31.3% from 1 test (PALOMA-3)	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[2]
50% across both tests	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[2]
Net cost to MBS							
ESR1 test cost							
BC: $1,500/test	**Redacted[3]**	**Redacted[3]**	**Redacted[3]**	**Redacted[3]**	**Redacted[3]**	**Redacted[3]**	**Redacted[4]**
$647.05/test[a]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]
$1,766.75/test[b]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[5]
Two-way sensitivity analyses							
ESR1 prevalence 47.7% across both tests							
$647.05/test[a]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]
$1,766.75/test[b]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[5]
ESR1 prevalence 50% across both tests							
$647.05/test[a]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]
$1,766.75/test[b]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[3]	Redacted[5]

Source: conducted by the evaluation group post-ESC at the request of ESCs and the department.

[a] An MBS fee of $647.05 sets the 85% (out-of-hospital) benefit to $550.00. This proposed fee is based on the Australian Clinical Laboratories (ACL) commercial ctDNA test for lung cancer, colorectal cancer and melanoma. The ACL test costs $550 to patients.

[b] An MBS fee of $1,766.75 sets the 85% (out-of-hospital) benefit to $1,664.35, applying MBS benefit rounding rules and a greatest permissible gap of $102.40. This proposed fee of $1,766.75 is based on the targeted consultation feedback, which stated that the indicated costs per test **redacted** is $1,664.33.

The applicant considered that the results presented in Table 15 were *ad-hoc* analyses conducted post-ESCs specifically for the purposes of informing the MSAC consideration and that interpretation of the results and their application should therefore be limited to seeking to understand the basis for the MSAC outcome and should not be used for any other purpose.

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] 10,000 to < 20,000

[3] $0 to < $10 million

[4] $10 million to < $20 million

[5] $20 million to < $30 million

15. Other relevant information

PASC noted consultation that raised equity concerns for rural/regional patients in that genetic testing is predominantly undertaken in major city centres. The submission advised that this would not be an issue as, although testing would be done in capital cities, the labs would take liquid biopsy samples from anywhere, with the applicant working with pathology groups across Australia. The submission estimated that the turnaround time for testing would be approximately 2 weeks. The submission's clinical expert advised that the recommendation of testing through liquid biopsy (rather than tissue biopsy) would be advantageous for rural/regional patients, as a tissue biopsy would require these patients to travel to cities/major centres, whereas a liquid biopsy can be taken as a blood sample from any location. PASC considered this to be an appropriate consideration for rural/regional patients and agreed with the submission that liquid biopsy was the preferred sample type (pp18-19, 1782 Ratified PICO Confirmation, August 2024 PASC meeting).

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues

- Proposed *ESR1* testing and new MBS item descriptor:
    - Testing methodology: The submission proposed specifying using next-generation sequencing (NGS) for ESR1 testing. The ESCs considered that both NGS and digital droplet polymerase chain reaction (ddPCR) would be appropriate testing methods. The ESCs noted the evidence the submission presented on the comparative test performance of NGS versus ddPCR or versus quantitative polymerase chain reaction (qPCR), as well as PASC's advice on using a method-agnostic item descriptor. The ESCs agreed with PASC that a method-agnostic item descriptor is more appropriate, noting the need to future-proof the item as other suitable methods may become available as technology advances.
    - Testing frequency: The proposed item descriptor did not mention re-testing, nor testing frequency. The ESCs noted PASC considered it appropriate to restrict testing frequency to once per 6 months as ESR1 variants may emerge as disease progresses. The ESCs agreed with PASC that testing every 6 months was reasonable but should only be in patients with previous negative test results. The ESCs considered it important to exclude retesting in patients with prior positive test results, to discourage use in monitoring treatment response rather than the proposed use of identifying patients likely to benefit from elacestrant treatment.
- Comparative test performance: The ESCs noted that the submission did not present any comparative evidence of concordance between the clinical utility standard (Guardant360® CDx assay) and *ESR1* assays that might be offered in Australia but considered that different NGS platforms all perform well, and are likely to be sufficiently concordant and identify patients likely to respond to elacestrant.

Economic issues

- The ESCs noted that the submission neither modelled the full population for testing nor captured re-testing explicitly and appropriately. The ESCs noted that varying the testing cost had little impact on the ICERs in the additional sensitivity analyses conducted post-ESC (Table 12).
- The ESCs noted that the submission did not consider both NGS and ddPCR in its cost modelling as PASC advised.

Financial issues

- The ESCs noted the commentary corrected the submission's under-estimation of total test numbers. The ESCs requested additional sensitivity analyses post-ESCs, using alternative testing costs.

Other relevant matters

- Implementation – readiness and availability of options for *ESR1* testing in Australia: **Redacted**. The ESCs noted that no relevant assay for testing is currently TGA-registered and raised concerns that pathology laboratories in Australia might not be ready to provide *ESR1* testing in ctDNA on the MBS.

ESCs discussion

The Joint MSAC Evaluation Subcommittee/PBAC Economics Sub Committee (hereafter referred to as the ESCs) noted that the integrated codependent application sought:

- Medicare Benefits Schedule (MBS) listing of next-generation sequencing (NGS) testing for activating estrogen receptor 1 (*ESR1*) variants in circulating tumour deoxyribonucleic acid (ctDNA) extracted from blood plasma (liquid biopsy) to determine eligibility for treatment with elacestrant in postmenopausal women or men with estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-), locally advanced or metastatic breast cancer (mBC), who have disease progression following at least one line of endocrine therapy (ET), including a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i).
- Pharmaceutical Benefits Scheme (PBS) General Schedule Authority Required (telephone/online) listing of elacestrant for the treatment of ER+/HER2- locally advanced or mBC with disease progression following at least one line of ET, including a CDK4/6i, in patients whose tumours have evidence of activating *ESR1* variants.

The ESCs noted and welcomed consultation feedback received from 3 organisations and 3 individuals. The ESCs noted that the feedback was supportive of listing elacestrant on the PBS for this population. The ESCs noted that feedback stated it was important to consumers that all patients who may benefit from treatment with elacestrant treatment would be identified by the proposed test. The ESCs also noted that the frequency of repeat testing was raised as an important issue that may affect access to the drug.

The ESCs noted that at least 70% of all newly diagnosed breast carcinomas are ER+/progesterone receptor positive (PR+)/HER2- and that, despite advances in treatment of ER+/HER2- mBC, patients ultimately progress on initial treatment with ET in combination with CDK4/6i, often due to *de novo* or emerging resistance. The ESCs noted that while some mBC patients (around 20%) progress rapidly within the first 6 months of first-line treatment with ET, many respond initially to treatment but develop resistance to therapy and progress over time (secondary resistance). The ESCs noted that *ESR1* variation is the most common mechanism of secondary resistance (up to 50%) and is a form of acquired resistance that occurs only following exposure to ET. The ESCs noted that *ESR1* variants are very uncommon (<1%) in primary untreated breast cancer and that longer exposure to ET during first-line metastatic treatment increases the chance of developing an *ESR1* variant during treatment. The ESCs considered the proposed testing in ER+/HER2- locally advanced or mBC patients who have disease progression following at least one line of ET (including a CDK4/6i) to be appropriate.

The ESCs noted that the application proposed ctDNA testing (from blood plasma) as opposed to solid tumour tissue testing. The ESCs noted that an individual patient may have multiple sites of metastases and that these would each need to be biopsied to determine *ESR1* status in the absence of a ctDNA test. The ESCs also noted that because clinically significant *ESR1* variants might emerge throughout the course of the disease in the metastatic setting, there is no role for archival tumour tissue testing at relapse. The ESCs noted that *ESR1* variants are subclonal and are therefore not always detected with tissue biopsy. Unlike sampling tumour tissue in a single region, use of ctDNA in the blood via liquid biopsy provides a representation of the spectrum of variants from tumour cells across all metastatic sites. The ESCs therefore considered ctDNA testing to be appropriate over solid tumour testing.

The ESCs noted that the application proposed using NGS for *ESR1* testing and specified this methodology in the proposed MBS item descriptor. PASC noted that other tests, i.e. digital droplet polymerase chain reaction (ddPCR) or quantitative PCR (qPCR), may also be used for

identifying *ESR1* variants. The ESCs noted that PASC advised that the assessment report should include data to support the exclusion of qPCR as an appropriate testing method.

The ESCs considered the exclusion of qPCR to be appropriate, as there are issues with using qPCR to detect *ESR1* variants in ctDNA, including a low range of variant detection, and the potential for false positives from cross-reactivity with similar sequences.

The ESCs noted that both ddPCR and NGS can detect ctDNA. ddPCR is highly sensitive and can detect low levels of ctDNA while NGS can analyse multiple driver genes simultaneously. The ESCs noted that there appears to be consensus that *ESR1* variant detection is similar across NGS and ddPCR tests. The ESCs noted that ddPCR can only be used for single-gene testing, whereas NGS can be used for multi-gene testing. ddPCR is also not currently widely available in Australian pathology laboratories. The ESCs considered that, because this application is only for single-gene testing (of *ESR1*), ddPCR would be an appropriate testing method if it became more widely available in Australia. The ESCs considered ddPCR would be cheaper than NGS if testing was performed in high volume centres. However, ESC advised that in Australia there will not be high volume centres performing ddPCR and these cost efficiencies will not be realised.

The ESCs noted that the test used in the pivotal EMERALD trial, Guardant360® CDx (the clinical utility standard), which uses NGS to detect *ESR1* variants in ctDNA extracted from blood (liquid biopsy), is not commercially available in Australia. The ESCs noted redacted.

The ESCs noted that none of the assays the submission provided that could potentially be used to detect *ESR1* variants in ctDNA in Australia are TGA-registered. The ESCs shared PASC's concern that pathology laboratories in Australia might not yet be ready for testing ctDNA from liquid biopsy. The ESCs noted the pre-sub-committee response (PSCR) stated that (i) 2 laboratories are expected achieve full NATA accreditation in Q2, 2025 and a 3rd laboratory is preparing for NATA accreditation; and (ii) all 3 laboratories participated in an *ESR1* external quality assessment (EQA) program (sourced internationally) in 2024. The ESCs considered that different NGS platforms should all perform well and are likely to be sufficiently concordant. The ESCs considered the different assays would identify patients who are likely to benefit from elacestrant.

The ESCs agreed with PASC that a method-agnostic item descriptor is more appropriate than the applicant's proposed descriptor specifying the use of NGS, noting that qPCR was likely not appropriate as an alternative testing methodology but ddPCR may be a suitable alternative if introduced more widely in Australia. The ESCs further considered that other testing approaches may emerge as a better methodology for *ESR1* variant detection than the current methods. The ESCs therefore advised that the new MBS item descriptor should not specify a testing method but rather remain method-agnostic, to allow for testing using ddPCR, NGS or other modalities that may develop in the future, thereby future-proofing the item.

The ESCs noted that the proposed MBS item descriptor did not mention re-testing, nor testing frequency. The ESCs noted that as *ESR1* variant(s) may emerge at each progression while on ET in the metastatic setting, testing for *ESR1* variants is relevant at each progression during the metastatic treatment course. The ESCs agreed with PASC that testing every 6 months was reasonable, but only for patients with previous negative test results. The ESCs considered it important to exclude retesting patients with prior positive test results, to discourage use of the proposed testing in monitoring treatment response, which is different from the proposed use of predicting treatment benefit with elacestrant. Once a patient has tested positive for *ESR1* variant(s), there is no need to repeat testing.

The ESCs considered that the applicant's nominated fee of $1,500 appeared reasonable for ctDNA testing using NGS, noting that the cost of ctDNA testing using NGS may be higher than

alternate test methodologies such as ddPCR. The ESCs considered that this higher fee appropriately reflected the additional complexity of extracting and purifying DNA from blood compared to tissue, as well as being related to the applicant's preferred test methodology (NGS).

The ESCs noted that a lower-fee option to cover other alternative ctDNA testing technologies was proposed by the department, at a revised fee of $647.05 (85% benefit = $550). The department considered this to be an appropriate schedule ctDNA technology-agnostic test in Australia. This fee was based on the Australian Clinical Laboratories (ACL) commercial ctDNA test for lung cancer, colorectal cancer and melanoma. The ACL test costs $550 to patients out-of-pocket (i.e. it is a patient-billed test since it is currently not rebated under Medicare)[21]. According to ACL educational materials, ACL uses three validated platforms: ddPCR, NGS and mass array[22]. Additional economic and financial sensitivity analyses were performed using higher and lower testing fees.

The ESCs noted that the proposed comparator for *ESR1* testing was no *ESR1* testing, and considered that this was appropriate.

The ESCs noted the submission did not anticipate any adverse events associated with *ESR1* testing compared to no testing. The ESCs noted that liquid biopsy is typically low risk and minimally invasive. The ESCs noted that in terms of treatment safety, elacestrant resulted in an increased number of adverse events, including an increase in Grade 3 or higher adverse events, which were most commonly gastrointestinal and musculoskeletal disorders such as nausea and back pain.

The ESCs noted that the key trial, EMERALD, demonstrated a statistically significant difference in progression-free survival (PFS) in the *ESR1* variant population treated with elacestrant compared to those treated with SOC, but that this was not observed in the non-*ESR1* variant population. The ESCs also noted that no significant difference was observed in overall survival (OS) for either population.

The ESCs noted that the submission's overall clinical claim was that 'in men and postmenopausal women with ER+/HER2- locally advanced or mBC, who have disease progression following at least one line of ET, including a CDK4/6i, and who test positive for an *ESR1* variant, elacestrant is superior to SOC in terms of effectiveness with a different and manageable safety profile'.

The ESCs considered that the claim of superior effectiveness was likely supported by the available evidence, but considered that the magnitude of treatment benefit may have been overestimated due to the choice of comparator, since in practice more SOC options would be available and in use. The ESCs considered that the safety of the proposed intervention to be inferior to that of SOC, noting the associated grade 3 adverse events.

The ESCs noted that the submission presented a cost-utility analysis (CUA) that evaluated the cost-effectiveness of elacestrant compared to SOC ET in ER+/HER2 mBC patients with *ESR1* variants and disease progression after 1-2 lines of ET. The ESCs agreed with the commentary that this was inappropriate and inconsistent with PBAC and MSAC guidelines which state that, for a co-dependent technology, the model structure should capture patients at the point of testing such that the incremental benefits and costs are included for those who are both positive and negative for the test. The ESCs also noted that the submission's approach was not consistent

[21] https://www.clinicallabs.com.au/about-us/doctor-media-releases/aspect-liquid-biopsy-analysis-of-circulating-tumour-dna-ctdna-in-cancer-patients-national/

[22] See Educational Module Part 2: (www.clinicallabs.com.au/aspect/)

with advice from PASC, which considered that cost modelling for both NGS and ddPCR methodology in the detection of *ESR1* variants should be included in the assessment.

The ESCs noted that the submission neither modelled the full population for testing nor captured re-testing explicitly. The submission applied one-off test costs to the elacestrant arm only ($3,144.74, based on an expected test cost of $1,500 and a prevalence rate of *ESR1* variants of 47.7%, i.e. 2.1 patients must be tested to identify one *ESR1* variant positive patient[23]). The submission argued that since the prevalence of *ESR1* variants in the EMERALD trial reflects patients who were 2nd and 3rd line post CDK4/6i treatment, this reflects the rate of *ESR1* variants across multiple lines of ET. Therefore, the submission argued that the economic model implicitly evaluates multiple rounds of testing, and it is not necessary to evaluate subsequent rounds of testing separately.

The ESCs noted that the methods used by the submission to determine testing costs reflect a scenario where eligible patients are only tested once following disease progression after 1 or 2 prior lines of therapy. This would not be consistent with the proposed clinical practice and MBS restriction, which allows testing at each episode of disease progression following first line treatment. As such, the ESCs considered that costs of testing applied in the model were underestimated. The ESCs considered the submission's current approach did not adequately capture the likely test costs, as it did not consider likely test accuracy and retesting. The ESCs considered that the economic model should be revised to capture the impact of incorporating 6-monthly testing for patients who previously tested negative.

The ESCs also requested an additional sensitivity analysis, post-ESCs, to show the impact of accounting for additional testing costs for patients who undergo re-testing following progression. The ESCs noted that there was uncertainty regarding the proportion of patients likely to test positive at the point of first progression and for each subsequent progression, as the EMERALD trial included patients who had multiple lines of previous treatments but *ESR1* testing results were only reported at study entry. The ESCs considered it was likely that there would be a diminishing number of additional patients who test positive at each subsequent progression, and this should be accounted for in the estimated cost of testing. The ESCs considered that the data from the PALOMA-3 trial (fulvestrant plus palbociclib vs fulvestrant alone) may be informative, as rates of *ESR1* variants were reported at baseline (25.1%) and end of treatment (31.3%, which would most closely match patients entering the EMERALD trial)[24]. The ESCs noted results of this sensitivity analysis showed that the ICER increased by Redacted%, from $55,000 to < $75,000 to $75,000 to < $95,000 per QALY gained (Table 12).

The ESCs requested additional analysis, post-ESCs, using the whole trial population from EMERALD versus the current use of only the *ESR1* variant subgroup to show the extent to which the ICERs would increase from the presented base case as the extent of treatment effect variation due to this biomarker is uncertain. The ESCs noted the evaluation group's advice that this was not possible as the submission's economic model was structured based on the *ESR1* variant subgroup only.

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[23] Note that the data presented in this sentence were provided by the applicant specifically for the purposes of informing the MSAC consideration. Interpretation of the data and their application should therefore be limited to seeking to understand the basis for the MSAC outcome and should not be used for any other purpose.

[24] O'Leary et al (2018) The Genetic Landscape and Clonal Evolution of Breast Cancer Resistance to Palbociclib plus Fulvestrant in the PALOMA-3 Trial *Cancer Discov* (2018) 8 (11): 1390–1403. https://doi.org/10.1158/2159-8290.CD-18-0264

The ESCs noted that the submission presented an estimated cost to the MBS of *ESR1* testing based on a unit price of $1,500 per test. The ESCs noted that the commentary corrected the financial estimates in the submission which underestimated the total test numbers and applied an 80% MBS benefit to costs on the basis that all items are out of hospital rather than an 85% benefit, with the greatest permissible gap ($102.40) also applied (cost to MBS per test=$1,397.60). The ESCs noted that, after correction, the commentary estimated the total test numbers to be 500 to < 5,000 in Year 1 and around 500 to < 5,000 per year in Years 2-6 of listing. The net cost to the MBS was estimated to be $10 million to < $20 million in the first 6 years of listing.

The ESCs requested additional sensitivity analyses, post-ESCs, using alternative unit prices for *ESR1* testing suggested by the department. Results are included in Table 15.

17. Applicant comments on MSAC's Public Summary Document

The applicant did not have any comments.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website