MSAC Application 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 AUSTRALIA PTY LTD

PICO Confirmation

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

Table 1 PICO for genetic testing to detect estrogen receptor 1 (*ESR1*) variants in patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-), locally advanced or metastatic breast cancer, to determine eligibility for treatment with PBS subsidised elacestrant

Component	Description
Population	**Test:** Men and postmenopausal women with ER+/HER2- locally advanced or metastatic breast cancer, who have disease progression following at least one line of endocrine therapy, including a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. **Treatment:** Those patients above who test positive for an *ESR1* variant.
Prior tests	Histological examination to confirm diagnosis of breast cancer Tests required to confirm stage of cancer (i.e. mammogram or ultrasound, lymph node assessment, computed tomography, magnetic resonance imaging) Tests required to confirm biomarker status (immunohistochemical evaluation for ER+/HER2-)
Intervention	**Test:** Testing for *ESR1* variants in circulating tumour DNA (ctDNA) extracted from blood (liquid biopsy) through next generation sequencing (NGS) **Treatment:** Elacestrant for patients found to have an *ESR1* variant
Comparator/s	**Test comparator**: No testing for *ESR1* variants **Treatment comparator:** Standard of care (SOC) second-line plus (2L+) therapies (PBS listed options include aromatase inhibitors (AIs) [anastrozole, letrozole, exemestane], everolimus-exemestane, tamoxifen, fulvestrant or chemotherapy)
Clinical utility standard	In the key clinical trial, EMERALD, the Guardant360® CDx test was used to identify *ESR1* variants in ctDNA extracted from blood (liquid biopsy) through NGS.
Outcomes	***Test outcomes*** *Test efficacy/effectiveness* • Diagnostic accuracy (Sensitivity, Specificity, PPV, NPV), test-retest reliability • Predictive validity of the test (distinguished from *ESR1* as a prognostic biomarker) *Other test-related considerations* • Number estimated to be tested at each line of therapy & diagnostic yield • Number needed to test (to identify one eligible case for treatment)

Component	Description
	• Test turn-around time • Test failure rate & need for repeat testing at the same line of therapy *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 [included in the clinical utility standard] vs digital droplet PCR (ddPCR) vs quantitative PCR (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* • Adverse events related to testing ***Treatment outcomes*** *Treatment efficacy/effectiveness* • Overall survival (OS) • Progression-free survival (PFS) • Overall response rate (ORR), complete response (CR), partial response (PR), stable disease (SD) • Health-related quality of life (HRQoL) *Treatment safety Outcomes* • Treatment-emergent and treatment-related adverse events ***Healthcare system*** • Total cost to the Medicare Benefits Schedule (MBS) for testing • Total cost to the Pharmaceutical Benefits Scheme (PBS) for treatment • Total cost to other healthcare services • Cost-effectiveness of test and treatment • Financial implications of test and treatment
Assessment questions	What is the safety, effectiveness, cost-effectiveness and total cost of genetic testing for *ESR1* variants and subsequent elacestrant therapy versus no testing for *ESR1* variants and SOC 2L+ treatment in men and postmenopausal women with ER+/HER2- locally advanced or metastatic breast cancer, who have disease progression following at least one line of endocrine therapy, including a CDK4/6 inhibitor?

Purpose of application

The codependent application requested:

- Medicare Benefits Schedule (MBS) listing of genetic testing to identify estrogen receptor 1 (*ESR1*) variants in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-), locally advanced or metastatic breast cancer, who have disease progression following at least one line of endocrine therapy, including a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, to determine eligibility for treatment with PBS subsidised elacestrant ; and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of elacestrant for the treatment of ER+/HER2- locally advanced or metastatic breast cancer in patients who have disease progression following at least one line of endocrine therapy, including a CDK4/6i, and test positive for an *ESR1* variant.

The applicant claims that genetic testing to identify *ESR1* variants, combined with targeted therapy with elacestrant, results in superior health outcomes compared to no testing and standard of care (SOC) second-line plus (2L+) treatment in patients with ER+/HER2- locally advanced or metastatic breast cancer, who have disease progression following at least one line of endocrine therapy, including a CDK4/6 inhibitor.

PICO criteria

Population

The proposed testing population comprises men and postmenopausal women with ER+/HER2- locally advanced or metastatic breast cancer, who have disease progression following at least one line of endocrine therapy, including a CDK4/6 inhibitor. The proposed treatment population is those patients above who test positive for activating *ESR1* variants.

Background

In Australia, breast cancer is the second most diagnosed cancer (most common in women) and the fifth most common cause of cancer death (second most common in women), with an estimated 20,640 new cases diagnosed and 3,214 deaths in 2022 (Cancer Australia, 2023).

Population breast screening services for Australian women aged between 50-74 years aim to detect early breast cancer (contained in the breast or spread to axillary lymph nodes only [Stage I and II]) (Australian Government Department of Health and Aged Care, 2023), which is curable in ~70–80% of patients (Harbeck et al., 2019). However, some patients (5-10%) will present with advanced breast cancer at diagnosis (comprising both inoperable locally advanced and metastatic breast cancer [Stage III and IV]) (Harbeck et al., 2019). Further, many patients with early breast cancer will progress to advanced breast cancer (20-30%) (Harbeck et al., 2019).

Advanced breast cancer is considered incurable, with the main goals of therapy to delay disease progression and prolong survival, while minimising treatment toxicity and preserving health-related quality of life (HRQoL) (Harbeck et al., 2019). In Australia, 5-year survival rates of ~81% (Stage III) and ~32% (Stage IV) have been reported (National Breast Cancer Foundation, 2024).

Management

On diagnosis of breast cancer, molecular markers (namely estrogen receptor [ER], progesterone receptor [PR] and human epidermal growth factor receptor 2 [HER2]) are routinely tested (through MBS items 72848 and 73061) to inform treatment options (Cancer Council Victoria and Department of Health Victoria, 2021; Harbeck et al., 2019). Tumours expressing ER and/or PR are categorised as hormone receptor-positive breast cancers, whilst tumours that do not express ER, PR or HER2 are categorised as triple-negative breast cancer (Harbeck et al., 2019). The most common molecular subtype is ER+/HER2-, also known as luminal breast cancer (Harbeck et al., 2019), which accounts for ~70% of cases of breast cancer in the US (National Cancer Institute, 2024b).

Except for patients with visceral crisis (imminent organ failure) in whom chemotherapy is recommended, endocrine therapy, with either aromatase inhibitors (AIs) or fulvestrant, plus a CDK4/6 inhibitor is the recommended SOC first-line treatment for patients with ER+/HER2- locally advanced or metastatic breast cancer (Gennari et al., 2021).

There is no optimal sequence of therapy following disease progression after first-line treatment; it is dependent on disease aggressiveness, organ function, biomarkers, which agents were used previously and consideration of associated toxicities (Gennari et al., 2021). In general, sequential endocrine therapy is recommended unless there is imminent organ failure (where chemotherapy is recommended), until all endocrine therapy options have been exhausted or where there is evidence of endocrine resistance (Gennari et al., 2021). However, clinical benefits from subsequent treatments are limited and diminish with each line of therapy, with poorer treatment responses associated with patients who acquire *ESR1* variants (Turner et al., 2020).

Endocrine resistance post disease progression from *ESR1* variants

ESR1 variants are a common cause of acquired resistance to endocrine therapy in patients with hormone receptor-positive advanced breast cancer, affecting up to 40-50% of patients (Brett et al., 2021). They are rarely detected prior to first treatment, occurring more frequently with longer exposure to endocrine therapy (Brett et al., 2021). The duration of exposure to endocrine therapy in first-line treatment has increased due to combination with CDK4/6 inhibitors, with median progression free survival ranging from 9.5 months to 28.1 months (Piezzo et al., 2020). As such, *ESR1* variants predominantly emerge during first-line treatment, although they may develop during any subsequent line of therapy; therefore, testing for *ESR1* variants is relevant at each episode of disease progression (Brett et al., 2021).

Elacestrant therapy

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

EMERALD enrolled 477 patients with ER+/HER2- locally advanced or metastatic breast cancer and disease progression after first- or second-line treatment with endocrine therapy and a CDK4/6 inhibitor, who were randomised to either elacestrant or SOC (per investigators choice of fulvestrant or AI monotherapy) (Bidard et al., 2022). This included 228 patients (47.8%) with identified *ESR1* variants (n=115 in elacestrant and n=113 in SOC), above the prespecified sample size of 220 patients (Bidard et al., 2022).

The trial population in EMERALD was closely aligned to the proposed test population for *ESR1* variants:

- Eligible patients were postmenopausal women or men aged 18 years or older with confirmed ER+/HER2- locally advanced or metastatic breast with disease progression after one or two prior lines of endocrine therapy.
- Progression on previous CDK4/6 inhibitor treatment in combination with an AI or fulvestrant was required.
- One previous chemotherapy regimen was permitted.
- Patients must have an ECOG performance status 0 or 1.

PASC agreed with the proposed test and treatment population as described in Table 1.

Estimates for size of the testing population

For investigative technologies, the incidence and prevalence of the target population for the test is required. A preliminary search conducted during PICO development found that much of the required data to estimate the size of the testing population in the Australian setting is unavailable (at least publicly).

PASC noted that there was no estimation of the size of the testing or treatment population in the pre-PASC PICO. The applicant has stated they will present estimates in the integrated codependent submission.

Prior tests

Patients with ER+/HER2- locally advanced or metastatic breast cancer would require prior testing before they would become eligible for *ESR1* variant testing. These prior tests include:

- biopsy and imaging (mammogram, ultrasound or magnetic resonance imaging [MRI]) to confirm diagnosis of breast cancer
- staging workup, which is guided by symptoms and may include clinical and ultrasound assessment of lymph nodes, computed tomography, bone scan, x-rays, magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography–computed tomography
- molecular diagnostic studies including:
    - immunohistochemical evaluation of ER status
    - immunohistochemical evaluation to determine HER2 status.

Intervention

Test

The proposed medical service is genetic testing to identify *ESR1* variants in circulating tumour DNA (ctDNA) extracted from blood (liquid biopsy) in patients with ER+/HER2- locally advanced or metastatic breast cancer who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor, to determine eligibility for treatment with PBS-subsidised elacestrant.

The applicant claimed testing for *ESR1* variants through liquid biopsy is a valid and preferable non-invasive alternative to tissue biopsy which allows longitudinal tracking of *ESR1* variants at multiple timepoints during the disease course without exposing patients to the risks related to invasive procedures (Sivakumar et al., 2022; Turner et al., 2020; Urso et al., 2021; Vidula et al., 2021). The European Society for Medical Oncology (ESMO) recommends that *ESR1* variants should preferentially be tested in ctDNA from liquid biopsy due to the very low risk of false positive findings compared to tissue biopsy (Pascual et al., 2022).

ESR1 variants can be identified in liquid biopsy through next-generation sequencing (NGS) or digital droplet PCR (ddPCR) methodologies. NGS can be used to detect multiple genetic changes (including rare or unknown variants), while ddPCR is used to detect known variants and has limited capacity of detecting only one variant per assay (Davidson et al., 2021). In the EMERALD clinical trial, the Guardant360® CDx test (Guardant Health, 2024) was used, which assessed *ESR1* variants using a NGS method.

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.

Pathology laboratories performing testing would need to be NATA-accredited, and as per other cancer biomarker genomic tests, competence in *ESR1* variant testing would be monitored via a Quality Assurance Program (QAP) by the Royal College of Pathologists of Australia (RCPA).

PASC noted that liquid biopsy was the preferred specimen type for ESR1 *variant testing, however 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 applicant advised they are 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.*

PASC noted the lack of Royal College of Pathologists of Australasia (RCPA) Quality Assurance Programs (QAP) [jointly the RCPAQAP] for ctDNA testing and queried how this would affect the proposed ctDNA testing. PASC noted the RCPAQAP are partnered with the European Molecular Genetics Quality Network (EMQN) for the provision of their 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 applicant advised that they have initiated contact with the RCPA to discuss details of a potential QAP in Australia. PASC acknowledged comments by the applicant's clinical expert that claimed liquid biopsy is the only appropriate source to detect* ESR1 *variants, as a localised tissue biopsy will not detect all circulating cancer cells. PASC noted that* ESR1 *variants often develop due to clonal evolution and that ctDNA has a higher incidence for the detection of* ESR1 *variants compared to tissue as circulating cancer cells can capture multiple clones. PASC considered that the use of a liquid biopsy was the more appropriate option to ensure the sample contains all circulating cancer cells and has a greater incidence for the detection of* ESR1 *variants. Therefore, PASC agreed with the applicant that liquid biopsy was the more appropriate testing sample for* ESR1 *variants. PASC noted the Australian Register of Therapeutic Goods (ARTG) listing for the test will be for the 'detection of* ESR1 *variant in blood plasma' (not tissue). Therefore, PASC considered it would be more appropriate for liquid biopsy to be specified in the proposed MBS item (to align with the ARTG listing). However, PASC considered that evidence to support the incremental benefits and risks for tumour testing with fresh tissue should still be provided and evaluated as part of the assessment report.*

<u>Treatment</u>

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

- Patients who have identified *ESR1* variants would be eligible to receive elacestrant treatment
- Patients without identified *ESR1* variants would receive SOC second-line plus (2L+) treatment

Elacestrant is a selective estrogen receptor degrader (SERD) that binds to estrogen receptor alpha (ERα), inducing degradation of Erα protein. Elacestrant can antagonise residual ER (wildtype or mutant) in tumour cells with its non-degradative antagonist function and is the first estrogen receptor antagonist to show significant efficacy in *ESR1* variant population (Bidard et al., 2022). In the key EMERALD trial, the use of elacestrant was associated with a significantly prolonged progression-free survival (PFS) compared to SOC 2L+ therapies in patients with ER+/HER2- locally advanced or metastatic breast cancer harbouring *ESR1* variants (Bidard et al., 2022). Further, in contrast to fulvestrant (which requires intramuscular injections), elacestrant has oral bioavailability and can be administered as a single daily tablet.

Comparators

Test

The nominated comparator is no testing.

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

The proposed test is expected to be used in addition to current (prior) tests.

Treatment

The comparator is SOC 2L+ treatment for patients with ER+/HER2- locally advanced or metastatic breast cancer.

Current PBS listed 2L+ treatment options include endocrine monotherapy (AIs [anastrozole, letrozole, exemestane], fulvestrant or tamoxifen), everolimus-exemestane or chemotherapy (if imminent organ failure or exhausted other endocrine treatments).

The applicant and the applicant's clinical expert confirmed the current SOC 2L+ treatment options available in Australia (as described in draft PICO confirmation).

PASC agreed with the proposed comparators for the test and treatment.

Clinical utility standard

In the EMERALD clinical trial, *ESR1* variant status was evaluated in ctDNA extracted from blood (liquid biopsy) using the Guardant360® CDx test (Guardant Health, 2024). The Guardant360® CDx uses next generation sequencing (NGS) and high throughput hybridisation-based capture technology to detect single nucleotide variants (SNVs), insertions and deletions (indels), copy number amplifications (CNAs) and fusions in a targeted panel of 55 genes. This includes full coverage of the *ESR1* gene, encompassing missense variants in the ligand-binding domain.

In the EMERALD trial, *ESR1* variants were defined as any missense variants in codon 310-547 (Bidard et al., 2022). *ESR1* variant status was not provided to study sites during treatment (Bidard et al., 2022).

The submission states that Guardant360® CDx test offers pathologists a ready-to-use solution which can minimise the level of technical failure and can easily be implemented in a laboratory. 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*.

In contrast, detecting *ESR1* variants through digital droplet PCR (ddPCR) methodology would require laboratories to assemble their own ddPCR assay. Such an assay would only detect a defined number of variants (essentially hotspot variants). As such, ddPCR may present some challenges regarding ease of use and implementation and utilization in routine clinical practice.

The applicant stated they are striving to facilitate *ESR1* testing in ctDNA extracted from blood (liquid biopsy) by leveraging established pathology laboratories (NATA accredited) across the country as reference labs for genomic testing. To achieve this goal, the applicant has initiated 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

PASC noted there are several 'ready to use' tests available for identifying ESR1 *variants that use a range of methodologies (NGS, ddPCR and real time PCR [qPCR]). The applicant cited anecdotal concerns around the validity of qPCR and high rate of false negatives. PASC considered that data to support the exclusion of qPCR as an appropriate testing method for* ESR1 *variants should be included as part of the assessment report.*

The PASC also heard that although there have been no direct comparisons of NGS vs ddPCR methodology on liquid biopsy specimens, NGS has a more comprehensive coverage of variants (100% vs 98% for ddPCR). PASC noted the pooled meta-analysis of ESR1 *testing from 16 studies using ddPCR (n=1684) or NGS (n=1,060) in HR+ breast cancer* performed by O. Najim et al. (2023). *PASC noted this study found no significant difference in both* ESR1 *mutation incidence between plasma and tissue; or* ESR1 *mutation incidence between ddPCR and NGS. PASC considered the results of this meta-analysis relevant to the concordance between testing methodologies and should be included and considered in the development of the assessment report.*

PASC noted the applicant's clinical expert advised that testing a small panel of variants through NGS was advantageous over ddPCR, which is more labour intensive as it targets only a limited number of specified variants at once. To get a similar level of coverage using ddPCR multiple tests would need to be run, meaning there is a risk that the ctDNA sample could be exhausted before all variants are tested for. The applicant's clinical expert advised that although NGS is more costly than ddPCR upfront, it is less costly overall as the test only needs to be run once.

Additionally, PASC queried the differences between the sensitivity of current NGS testing and the requirements/adaptations for the proposed ctDNA test. PASC considered that the assessment report should explore what adaptations are required for the proposal to test ctDNA via the NGS methodology.

PASC noted the EMERALD trial used NGS testing however, PASC considered that it is the purpose of the assessment to assess the evidence and comparative testing performance across all appropriate testing methodologies.

Outcomes

The pivotal EMERALD trial provides direct evidence of the clinical utility of using *ESR1* variant status as a predictive biomarker for the benefit of treatment with elacestrant in patients with ER+/HER2- locally

advanced or metastatic breast cancer who have disease progression following at least one line of endocrine therapy, including a CDK4/6 inhibitor.

The following outcomes are relevant for MSAC decision making:

Test outcomes

Test efficacy/effectiveness

- Diagnostic accuracy (Sensitivity, Specificity, PPV, NPV), test-retest reliability
- Predictive validity of the test (distinguished from *ESR1* as a prognostic biomarker)

Other test-related considerations

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

Comparative performance of ESR1 variant testing methods

- Concordance between *ESR1* variant testing assays (NGS vs ddPCR) and testing source (ctDNA vs tissue sample at time of disease progression)
    - Positive percent agreement (PPA) and negative percent agreement (NPA)

Change in clinical management from testing

- Percentage of patients changing treatment plan

Testing safety outcomes

- Adverse events related to testing

Treatment outcomes

Treatment efficacy/effectiveness

- Progression-free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR), complete response (CR), partial response (PR), stable disease (SD)
- Health-related quality of life (HRQoL)

Safety Outcomes

- Treatment-emergent and treatment-related adverse events

Healthcare system

- Total cost to the Medicare Benefits Schedule (MBS) for testing
- Total cost to the Pharmaceutical Benefits Scheme (PBS) for treatment
- Total cost to other healthcare services
- Cost-effectiveness of test and treatment
- Financial implications of test and treatment

PASC noted that concordance between ESR1 *variant testing sources (liquid biopsy vs tissue biopsy) would no longer be necessary given that it had been agreed that the testing source would be liquid biopsy only however, PASC considered that the comparative performance of ctDNA vs tumour testing should be presented in the assessment.*

PASC agreed with all other proposed test and treatment outcomes.

PASC noted advice from the applicant that the risk of false negatives through NGS would be very low, specifically there had been no incidence of a false negative yet in more than 5000 patients tested.

The primary endpoint in EMERALD was PFS in all patients and in patients with identified *ESR1* variants, assessed by blinded independent central review (BICR). Key secondary endpoints were OS in all patients and in patients with identified *ESR1* variants. Other secondary end points included objective response rate, duration of response and clinical benefit rate ([CBR] the proportion of patients who experienced either a confirmed complete or partial response, or stable disease at ≥ 24 weeks from random assignment) and safety and tolerability.

PASC considered that currently only an interim analysis of OS is reported from the EMERALD trial; updated OS results, as well as extended analyses of the safety and tolerability of elacestrant treatment and HRQoL data collected from the EMERALD trial (if applicable) are to be considered by the applicant for the assessment report.

Assessment framework (for investigative technologies)

An initial assessment framework linking genetic testing for *ESR1* variants to the relevant health outcomes is presented in Figure 1.

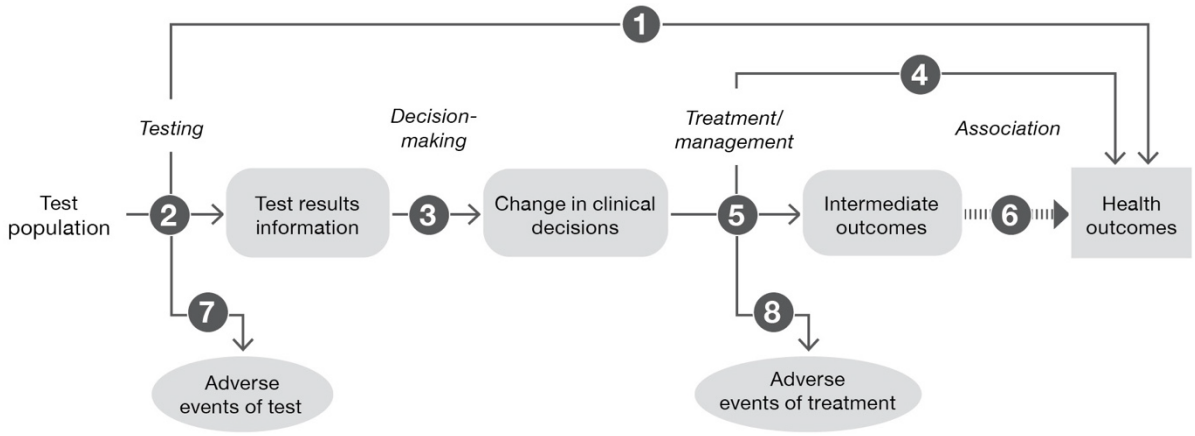

Figure 1 Generic assessment framework showing the links from the test population to health outcomes

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

Assessment questions for a claim of superiority:

1. Does the use of genetic testing for *ESR1* variants in place of no testing result in the claimed superior health outcomes?

2. What is the accuracy of NGS (sensitivity, specificity) using ctDNA extracted from blood (liquid biopsy)? How does this differ from ddPCR and qPCR methodology? What are the implications of discordance between these methodologies?

3. Incremental benefits and risks of ctDNA testing compared to tumour testing for *ESR1* variants?

4. Does the availability of new information (*ESR1* variants) lead to a change in management of the patient?

5. Do the differences in management derived from testing (elacestrant treatment for patients with *ESR1* variants) result in the claimed superior health outcomes (OS, PFS, HRQoL)?

6. Do the differences in management derived from testing (elacestrant treatment for patients with *ESR1* variants) result in the claimed superior surrogate outcomes (complete response, ORR)?

7. Is the observed chance in surrogate (complete response, ORR) associated with the concomitant chance in claimed health outcomes (PFS, OS, HRQoL)? And how strong is the association?

8. What are the adverse events associated with testing for *ESR1* variants compared to a no testing strategy?

9. What are the adverse events associated with elacestrant treatment for patients with *ESR1* variants? What are the adverse events associated with SOC for patients without *ESR1* variants?

PASC agreed that the described assessment framework was appropriate, however recommended that the following should occur: noting that concordance between liquid biopsy vs tissue biopsy was no longer required; and to assess the incremental benefits and risks of ctDNA testing compared to tumour testing for ESR1 *variants.*

Clinical management algorithms

Current clinical management algorithm (comparator)

Australian clinical practice is informed by international treatment guidelines, including those from the US (National Comprehensive Cancer Network [NCCN]) (NCCN, 2024) and Europe (European Society for Medical Oncology [ESMO]) (ESMO, 2024). Except for patients with visceral crisis (imminent organ failure) in whom chemotherapy is recommended, endocrine therapy, with either AIs or fulvestrant, plus a CDK4/6 inhibitor is the recommended SOC first-line treatment for patients with ER+/HER2- advanced breast cancer (Gennari et al., 2021).

CDK4/6 inhibitors include the PBS listed drugs palbociclib, ribociclib and abemaciclib (Australian Government Department of Health and Aged Care, 2024b, 2024g, 2024h). There have been no head-to-head comparisons of these three drugs; while their efficacy in treatment of advanced breast cancer appears similar, their toxicity profiles are slightly different (Gennari et al., 2021). As such it is recommended to switch CDK4/6 inhibitors if severe toxicity develops (Gennari et al., 2021).

Endocrine monotherapy in the first-line setting is reserved for patients with comorbidities or a performance status that prevents use of CDK4/6 inhibitors (Gennari et al., 2021). In patients who required first-line treatment with chemotherapy due to imminent organ failure or did not have access to a CDK4/6

inhibitor, it is clinically acceptable to use endocrine therapy plus a CDK4/6 inhibitor as a second-line therapy in the case of progressed disease (Gennari et al., 2021).

In patients who relapse after SOC first-line treatment, ESMO guidelines recommend determination of somatic *PIK3CA* and *ESR1* variants, as well as germline *BRCA1/2* and *PALB2* variants (Gennari et al., 2021). Genetic testing for germline *BRCA1/2* and *PALB2* variants is currently MBS listed for patients with breast cancer for whom clinical and family history criteria place the patient at greater than 10% risk of having these variants (limited to one test per cancer diagnosis) (item number 73297) (Australian Government Department of Health and Aged Care, 2024a). There is currently no MBS listed items for genetic testing for somatic *PIK3CA* or *ESR1* variants.

Selection of second and subsequent lines of therapy (chemotherapy vs further endocrine therapy) is dependent on disease aggressiveness, organ function and consideration of associated toxicities (Gennari et al., 2021). No optimal sequence of therapy after progression on CDK4/6i has been established; it is dependent on which agents were used previously, duration of response to prior endocrine therapy, biomarkers, disease burden, prior treatment and patient preference (Gennari et al., 2021). In general, sequential endocrine therapy is recommended unless there is imminent organ failure (where chemotherapy is recommended), until all endocrine therapy options have been exhausted or where there is evidence of endocrine resistance (Gennari et al., 2021). Current PBS listed options for 2L+ treatment include AIs (anastrozole, letrozole, and exemestane) or fulvestrant (if not already used in previous lines of therapy), everolimus-exemestane or tamoxifen (Australian Government Department of Health and Aged Care, 2024c, 2024f, 2024d, 2024e, 2024i).

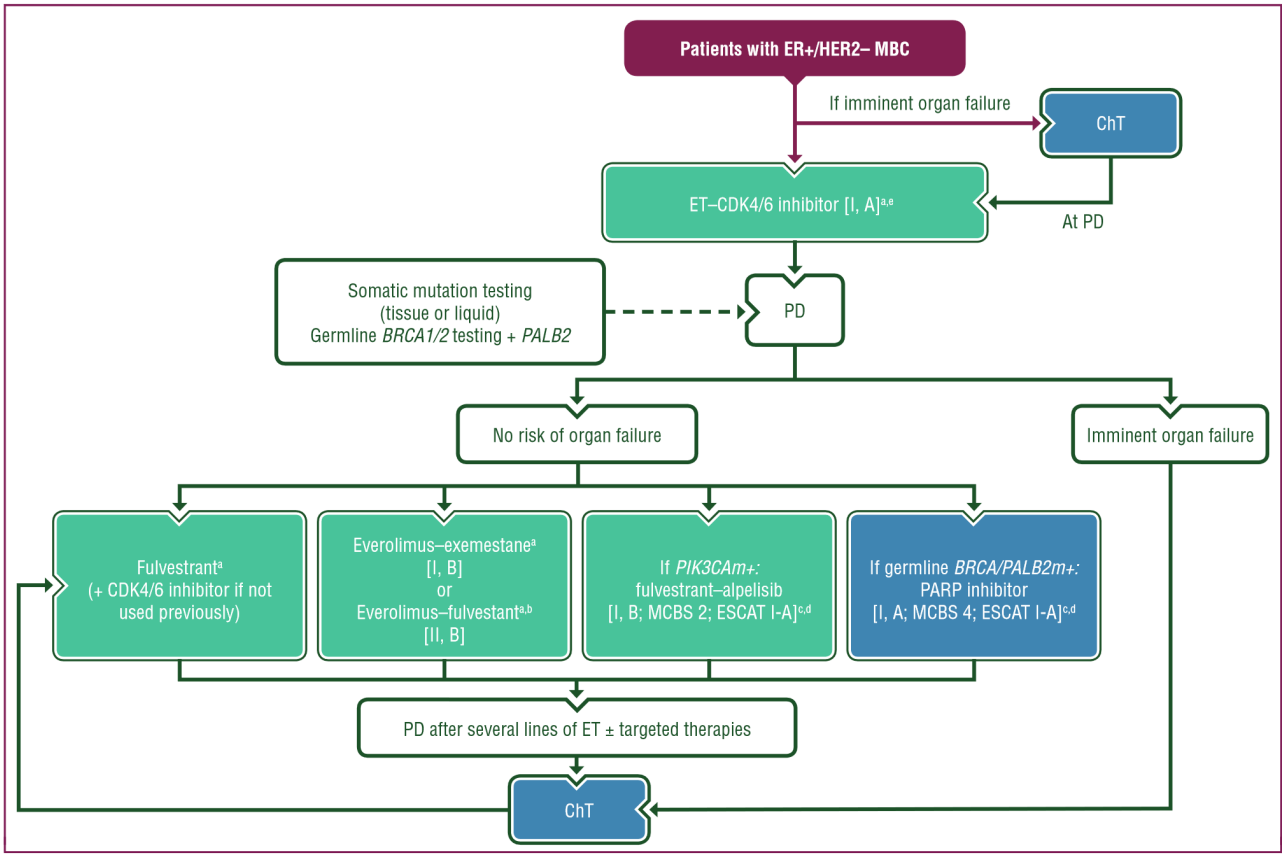

Figure 2. ESMO Clinical Practice Guidelines for patients with ER+/HER2- advanced Breast Cancer

Source: Figure 2, Gennari et al 2021

AI =aromatase inhibitor; CDK4/6 = cyclin-dependent kinase 4 and 6; ChT = chemotherapy; EMA= European Medicines Agency; ER= estrogen receptor; ESCAT = ESMO Scale for Clinical Actionability of Molecular Targets; *ESR1* = estrogen receptor 1; ET = endocrine therapy; FDA = Food and Drug Administration; HER2 = human epidermal growth factor receptor 2; m = mutation; MBC = metastatic breast cancer; MCBS = ESMO-Magnitude of Clinical Benefit Scale; OFS = ovarian function suppression; *PALB2* = partner and localiser of *BRCA2*; PARP = poly (ADP-ribose) polymerase; PD = progressive disease; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

[a] OFS if the patient is premenopausal.

[b] Preferred if the patient is *ESR1* mutation positive [ESCAT score: II-A].[d]

[c] ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluationforms-v1.1).

[d] ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.

[e] If relapse <12 months after end of adjuvant AI: fulvestranteCDK4/6 inhibitor[a]; if relapse >12 months after end of adjuvant AI: AI-CDK4/6 inhibitor[a].

The applicant confirmed that the description of current clinical management provided is broadly reflective of Australian clinical practice.

Proposed clinical management algorithm (intervention)

In recently updated ESMO and NCCN clinical guidelines, elacestrant has been added as a recommended treatment option for postmenopausal females or adult males with ER+/HER2- locally advanced or metastatic breast cancer with *ESR1* variants after disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor (ESMO, 2024; NCCN, 2024).

As such, the clinical management algorithm proposed in the application (Figure 3) is consistent with current clinical guidelines. Endocrine therapy combined with a CDK4/6 inhibitor remains the recommended first-line treatment option, with testing for *ESR1* variants indicated at each incidence of disease progression to inform subsequent lines of therapy (elacestrant vs SOC).

However, the proposed clinical management algorithm does not include testing for other genetic variants (*PIK3CA, BRCA1/2 and PALB2*) which is recommended following disease progression after first-line therapy (Gennari et al., 2021). In contrast to *ESR1*, these variants are not acquired in response to endocrine therapy and therefore would only require a single test to be detected.

Additionally, the proposed clinical management algorithm does not detail therapy options post disease progression after treatment with elacestrant.

PASC presented an updated clinical management algorithm which includes the option of chemotherapy at any line of therapy (if imminent organ failure/visceral crisis), as well as testing for other actionable variants (e.g. BRCA1/2, PALB2 *[MBS item 73297]) after disease progression following 1st line therapy. PASC noted that the applicant agreed with the updated proposed clinical management algorithm (Figure 3).*

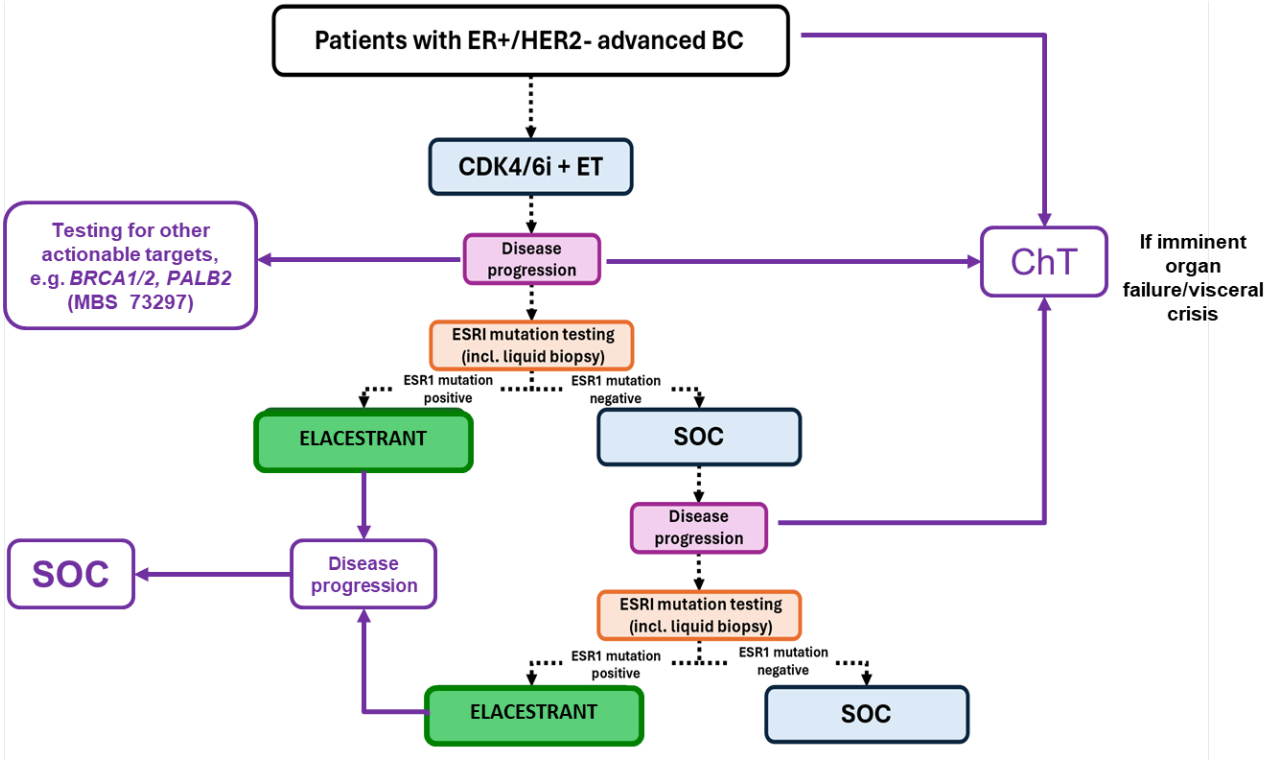

Figure 3. Clinical management algorithm with introduction of intervention
Source: Figure 1, p16 of the submission
Abbreviations: BC = breast cancer; *BRCA1/2* = Breast Cancer gene 1/2; CDK4/6i = Cyclin-dependent kinase 4/6 inhibitors; ChT = chemotherapy, ER+/HER2- = estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative; *ESR1* = estrogen receptor 1; ET = endocrine therapy; MBS = Medicare Benefit Schedule; *PALB2* = Partner and localizer of *BRCA2*; SOC = standard of care.

Proposed economic evaluation

The overall clinical claim is that the proposed codependent technologies (genetic testing for *ESR1* variants and elacestrant therapy) is superior in terms of effectiveness, with a well-tolerated and manageable safety profile that maintains HRQoL, compared to no testing and SOC 2L+ treatment in patients with ER+/HER2- locally advanced or metastatic breast cancer who have disease progression following at least one line of endocrine therapy, including a CDK4/6 inhibitor.

This claim is based on preliminary results from the phase III clinical trial EMERALD, which demonstrated that patients treated with elacestrant had prolonged progression-free survival (PFS) compared to patients

treated with SOC endocrine monotherapy (fulvestrant or an AI) (hazard ratio = 0.70, 95% CI 0.55 to 0.88, p=0.002). A sub-group analysis for patients with *ESR1* variants revealed an even greater treatment effect (hazard ratio = 0.55, 95 CI 0.39 to 0.77, p=0.0005), indicating that overall improvements in PFS related to elacestrant therapy were largely attributable to treated patients with *ESR1* variants. Treatment-related adverse events leading to treatment discontinuation were 3.4% in the elacestrant arm compared to 0.9% in SOC, while nausea of any grade occurred in 35% of patients receiving elacestrant compared to 18.8% in SOC.

Based on the clinical claim and the available evidence, the appropriate type of economic evaluation would be a cost-utility analysis (Table 2).

PASC agreed that, based on the evidence from the EMERALD trial, claims that testing for ESR1 *variants and treatment with elacestrant is superior in terms of effectiveness and inferior in terms of safety compared to no testing and SOC. Therefore, PASC considered that a cost utility analysis (CUA) would be the most appropriate type of economic evaluation. PASC considered that cost modelling for both NGS and ddPCR methodology in the detection of* ESR1 *variants should be included in the assessment. PASC considered that the appropriateness of including qPCR in the cost modelling would be dependent on the additional data (supplied by the applicant) to support the claim of poor performance of qPCR.*

A preliminary search conducted during the PICO development identified one modelled cost-utility analysis (from a US payer perspective) comparing elacestrant to SOC as second- and third-line treatment for patients with pretreated ER+/HER2- advanced breast cancer, utilising effectiveness and safety data from EMERALD and utility values derived from published studies (Zeng et al., 2023). However, this study did not consider the additional costs associated with testing for *ESR1* variants for elacestrant therapy (compared to no testing and SOC).

Table 2 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

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

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

The proposed MBS item descriptor for *ESR1* variant testing in patients with advanced breast cancer is shown in Table 3.

Table 3. Proposed MBS item descriptor

Category 6 – Pathology Services
MBS item *XXXX Group P7 - Genetics A test of ctDNA extracted from blood plasma for the detection of *ESR1* missense variants in an altered tumour, in a patient with: • 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. As requested by a specialist or consultant physician, to determine eligibility for treatment with elacestrant under the Pharmaceutical Benefits Scheme (PBS) Applicable once in any six month period.
Fee: $XX Benefit: 75% = $XX 85% = $XX

PASC considered proposed changes to the MBS item descriptor, namely that the source for testing (ctDNA extracted from blood plasma vs tissue biopsy) should be agnostic and that the item should be futureproofed for the possible inclusion of other variants and treatments (i.e. the item is drug agnostic).

PASC agreed with the applicant that the source of testing should be specified as 'ctDNA extracted from blood plasma', as tissue biopsy is unlikely to be appropriate for testing ESR1 *variants. The applicant and the applicant's clinical expert also agreed that it would be sensible to futureproof the MBS item descriptor for potential inclusion of other variants and treatments.*

PASC noted the proposed MBS item descriptor does not specify the testing methodology to be used for identifying ESR1 *variants. PASC noted the department preference for method agnostic items but considered that justification for test methodology specific items should be included in the assessment.*

PASC considered whether there should be a limit on the number/frequency of testing in the MBS item descriptor, noting patients in the EMERALD trial were limited to those who had disease progression following one or two lines of prior therapy. The applicant advised that testing would only occur on disease progression; it is estimated that approximately 40-50% of patients will acquire ESR1 *variants, with most occurring after progression on first- or second-line therapy. It was estimated that the average time between tests for* ESR1 *would 6-8 months (after disease progression following first line therapy). PASC considered it was appropriate to include a restriction for the limit/frequency of testing to be once every 6 months.*

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

The application did not propose an MBS fee. For comparison, 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) are priced at $1200.

PASC noted that no fee had been proposed yet by the applicant. An estimate of a $400 fee was made, based on a currently available test of ESR1/PIK3CA/ERBB2 *&* AKT1 *variants from Sonic Genetics (which uses*

ddPCR methodology) and similar single genetic items on the MBS. PASC noted the applicant advised that the proposed fee would likely be higher than $400 using a small NGS panel. PASC noted that the applicant confirmed a proposed MBS fee will be provided in the assessment report.

Elacestrant is currently undergoing TGA evaluation, with the applicant intending to submit a codependent application to the Pharmaceutical Benefits Advisory Committee (PBAC) for the March 2025 meeting (12/03/25).

Summary of public consultation input

PASC noted and welcomed consultation input from 2 organisations, the organisations that submitted input were:

- Rare Cancers Australia (RCA)
- Australian Genomics

The consultation feedback received was supportive of public funding for genetic testing to detect *ESR1* mutations in patients with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, to determine eligibility for treatment with PBS subsidised elacestrant.

Consumer Feedback

Rare Cancers Australia stated that patients, particularly mothers caring for families, face exhaustion, physical changes such as hair loss, vulnerabilities, and gruelling treatments that may include procedures such as single and double mastectomies. This is often in addition to financial difficulty due to needing time off or having to cease work to travel and receive treatment.

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included providing access to targeted therapy in a population with limited treatment options, considerable improvements in quality of life (increased progression-free-survival) and reduced financial burden to patients and their families.

Australian Genomics commented on the disadvantages of public funding and barriers to implementation, which included equity of access to specialised medical services in general, underrepresentation of Indigenous Peoples in clinical trials, the cost of setting up either digital droplet polymerase chain reaction (ddPCR) or next generation sequencing (NGS) diagnostic testing and incorporating this into laboratory workflows and Australian cancer care guidelines.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included specialist consultants as part of medical oncology teams and a registered molecular pathologist responsible for detection, diagnosis and reporting.

PASC noted consultation that raised equity concerns for rural/regional patients in that genetic testing is predominantly undertaken in major city centres. The applicant 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 applicant estimated that the turnaround time for testing would be approximately 2 weeks. The applicant'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 applicant that liquid biopsy was the preferred sample type.

PASC also heard from the consumer member that there was a query as to whether genetic counselling would be required. The clinical expert advised there would be no need for genetic counselling as ESR1 *variants are somatic (non-inheritable). PASC agreed with the applicant and considered that considerations for genetic counselling was not required.*

Additionally, PASC noted that there was an under representation of First Nations patients in the provided clinical trials and queried whether testing in this cohort would require any additional measures to detect ESR1 *variants. PASC noted that the applicant did not provide any additional information in relation to this point and considered that the assessment could address these issues.*

Indication(s) for the proposed medical service and clinical claim

The consultation feedback agreed with the proposed population. Australian Genomics considered the population was appropriate and well defined and Rare Cancers Australia state that this is a group with a higher level of unmet clinical need and limited treatment options.

Consultation feedback agreed with the proposed comparator.

Australian Genomics generally agreed with the clinical outcomes, stating that certainty around the EMERALD trial results demonstrating increased progression free survival is strengthened by the incorporation of *ESR1* as a biomarker in the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines and adoption of the proposed service by other countries including Europe and the US. Australian Genomics stated a potential outcome not mentioned in the application was managing patient expectations as different *ESR1* mutations can relate to varying degrees of drug effectiveness in different clinical presentations.

Cost information for the proposed medical service

Australian Genomics commented on the item descriptor, requesting clarity on the number of times the test can be performed, noting method of testing was not described, potentially allowing other genes of interest to be tested in parallel. Australian Genomics stated that liquid biopsy is the preferred sample as it is less invasive and more efficient at detecting the tumour microenvironment as *ESR1* mutations are acquired during endocrine therapy and that that archived material is not recommended for testing – due to subclonality, polyclonality and the distinctive effects of specific *ESR1* variants. However, they further stated that different cell free DNA shedding rates and circulating tumour cell release may differ depending on tumour microenvironment.

Australian Genomics noted no fee was provided for consultation.

Next steps

PASC agreed that the applicant was ready to proceed with the assessment report.

Applicant Comments on Ratified PICO

Applicant has no comments.

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