

MSAC Application 1782

Genetic testing to detect estrogen receptor 1 (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

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:

The application requests Medicare Benefits Schedule (MBS) funding for testing to identify estrogen receptor 1 gene (ESR1) activating mutations in patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer (a/mBC), who have disease progression following at least one line of endocrine therapy (ET), including a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i), to determine Pharmaceutical Benefits Scheme (PBS) eligibility for elacestrant (Orserdu[®]), a new generation, selective estrogen receptor degrader (SERD) to inhibit ER signalling.

The test for ESR1 mutations uses circulating tumour DNA (ctDNA) extracted from blood plasma (obtained via a liquid biopsy) for the detection of ESR1 mutations in an altered tumour.

Elacestrant is currently undergoing TGA evaluation for treatment in this population.

Breast cancer (BC) is the most commonly diagnosed cancer among women in Australia, with approximately 57 Australians diagnosed each day (National Breast Cancer Foundation, 2024). In 2022, there were an estimated 20,640 new cases diagnosed and 3,214 deaths from BC (Cancer Australia, 2023).

Advanced breast cancer comprises both locally advanced (inoperable) and metastatic disease (a/mBC). Some patients (5-10%) present with a/mBC disease at diagnosis, and many with early BC eventually progress to a/mBC (20% to 30%) (Harbeck, et al., 2019; Peart, 2017; Vera-Llonch, et al., 2011; Globocan, 2020). Although treatment is available, a/mBC remains incurable with a median survival of approximately 3 years and a 5-year survival rate of around 25-36% (Cardoso et al 2018; (SEER, 2022; Valachis, et al., 2022; Grinda, et al., 2021; Menarini, 2023).

Several prognostic indicators for BC have been identified including HER2, ER and progesterone receptor (PR) (ER and PR are also collectively referred to as hormone receptors [HR]). The most common subtype is ER-positive, HER2-negative (ER+/HER2-), accounting for about 70% of cases of BC (Howlander, et al., 2014; Iwase, et al., 2021; Anderson, et al., 2017; Zhou, et al., 2023). Patients with ER+/HER2- a/mBC ultimately experience disease progression due to poor treatment outcomes, which diminish with each line of therapy.

ET plus a CDK4/6i is the standard of care (SOC) in first line (1L) ER+/HER2- a/mBC. However, tumours eventually develop resistance to endocrine therapies (Zhao, Hanson, Zhang, Zhou, & Cha-Silva, 2023; Burstein, et al., 2021; Burstein, 2020; Osborne & Schiff, 2011). ESR1 mutations represent a type of acquired resistance in up to 40-50% of patients after initial ET in the metastatic setting (Brett, Spring, Bardia, & Wander, 2021; Santiago Novello, Lobo, Silveira Vilbert, Sanches, & Cesca, 2023). ESR1-mutations alter the conformation of the estrogen receptor (ER) ligand binding domain that results in ligand independent ER activation and constitutive ER signalling that promotes tumour growth and resistance, predominantly after ET (Brett, Spring, Bardia, & Wander, 2021; Santiago Novello R. G., 2023; Jhaveri, 2023; Lin, 2023; Bhave, et al., 2023; Toy, et al., 2013).

While ESR1 mutations in a/mBC *per se* can be prognostic in that patients with these mutations have poorer outcomes (ESR1-mutations drive a more aggressive metastatic phenotype), **ESR1 activating mutations are also a predictive biomarker for the benefit of elacestrant.**

Elacestrant is an estrogen receptor antagonist that binds to estrogen receptor alpha (ER α) inducing degradation of ER α 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 mutant population (Bidard, et al., 2022). In the phase III EMERALD trial, the use of elacestrant was associated with a significantly prolonged progression-free survival (PFS) in patients with ER+/HER2- a/mBC harbouring ESR1 mutations (Bidard, et al., 2022).

The EMERALD trial results with elacestrant demonstrated the clinical utility of ESR1 mutational status using ctDNA extracted from blood (liquid biopsy) and therefore its predictive value to guide clinicians in innovative and personalised therapeutic decisions with elacestrant (Bidard, et al., 2022). Using ESR1 mutations as predictive biomarker for treatment with elacestrant optimises treatment outcomes and informs physicians about the likelihood of clinical benefit in ER+/HER2- a/mBC patients (Bidard, et al., 2022).

ESR1-mutations usually emerge during 1L ET in a/mBC and continue to increase with longer ET exposure in subsequent lines of therapy, leading to endocrine resistance to AIs or fulvestrant that lead to poorer outcomes (Brett, Spring, Bardia, & Wander, 2021)(Toy, et al., 2013; Jeselsohn, et al., 2014; Jeselsohn, et al., 2018; Allouchery, et al., 2018; Schiavon, et al., 2015; Clatot, et al., 2020; Chardarlapaty, et al., 2016; Turner, et al., 2020; Zundeleovich, 2020; McDonnell, Norris, & Chang, 2018). This type of mutation is unlikely to be detectable on diagnosis of early BC where this mutation is rare (present in 1-3% of cases) (Zundeleovich, 2020). An ESR1 mutation may develop at each disease progression, and therefore testing for ESR1 mutations is relevant at each progression during the metastatic treatment course (Brett, Spring, Bardia, & Wander, 2021; Allouchery, et al., 2018). Indeed, Guidelines recommend routine testing for the emergence of ESR1-mut at each disease progression to help inform clinical treatment decisions (Burstein, DeMichele, Somerfield, & Henry, 2023; Lee, Park, Song, Jeon, & Jeong, 2020; Gennari, et al., 2021).

Consequently, an archived sample from a tissue biopsy at time of first diagnosis of BC is not adequate to detect these activating mutations. ctDNA extracted from blood obtained via liquid biopsy after exposure to ET is the most suitable specimen to determine ESR1 mutational status:

- i. The clinical evidence base for elacestrant, the pivotal EMERALD trial, utilised only a liquid biopsy as biological specimen to assess the presence of a ESR1 mutation in ctDNA (extracted from blood)
- ii. The biology of the tumour
 - a. ESR1 mutations often emerge at the time of first or subsequent progressions post ET/AI treatment (Brett, Spring, Bardia, & Wander, 2021) (Jeselsohn, et al., 2014)
 - b. The frequency of ESR1 mutations changes during the course of the disease (Cogliati, et al., 2022) (Brett, Spring, Bardia, & Wander, 2021) (Jeselsohn, et al., 2014) (Jeselsohn, et al., 2018) (Bidard, et al., 2022) (Allouchery, et al., 2018)
 - c. Liquid biopsy has been shown to be sensitive for identifying this mutation
 - d. Higher prevalence of actionable mutations is detected in liquid biopsy vs. tissue biopsy (Dustin, Gu, & Fuqua, 2019; Vidula, et al., 2021; Sivakumar, et al., 2022).
- iii. Archived tissue is not suitable for ESR1 mutational testing (Bardia, et al., 2022)
- iv. In addition to the predictive value of ESR1 mutations in ctDNA extracted from blood, the ease of use and timing of tests are to be considered. Indeed, repeated tests may be required (after 2L+ ET treatment) and multiple tissue biopsies are not practical and inconvenient for a patient.
 - a. Testing for ESR1 mutations should occur at each progression during a/mBC treatment course (Jeselsohn, et al., 2014; Jeselsohn, et al., 2018; Allouchery, et al.,

2018; Schiavon, et al., 2015; Brett, Spring, Bardia, & Wander, 2021), if not detected previously.

The proposed health technology

Testing for ESR1 mutations in ctDNA extracted from blood (liquid biopsy) to determine eligibility for treatment with elacestrant, a SERD to inhibit ER signalling, in patients with ER+/HER2- a/mBC, who have disease progression following at least one line of ET, including a CDK4/6i.

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

ER+/HER2- a/mBC is an incurable disease, therefore the main goals for treatment are delaying disease progression and prolonging survival, while minimising treatment toxicity and preserving health related quality of life (HRQoL) for the patient (Smith, 2006; Harbeck & Gnant, 2017; Waks & Winer, 2019).

An optimal care pathway, including diagnosis, staging and treatment planning, has been endorsed by the Australian Government and the Cancer Council (Cancer Council Victoria and Department of Health Victoria, 2021). The optimal care pathways describe the standard of care that should be available to all cancer patients treated in Australia including presentation, initial investigations, referral, and treatment, which consists of surgery, chemotherapy and systemic therapy and/or radiation.

Australian clinical practice is informed by international treatment guidelines, including those from NCCN and ESMO. With the exception of patients with visceral crisis in whom chemotherapy is recommended, ET + CDK4/6i is recommended as the mainstay 1st line treatment (Gennari, et al., 2021). In subsequent lines (2L+), guidelines recommend sequential ET until exhaustion of ET-based options or evidence of ET resistance (ESMO, 2023a). The optimal sequence of endocrine-based therapy following disease progression on ET + CDK4/6i depends on duration of response, biomarkers, disease burden, prior treatment and patient preference (ESMO, 2023b).

Approximately 20% of a/mBC patients progress rapidly on initial ET (i.e., primary resistance, with disease progression within the first 6 months of first-line ET for a/mBC according to current definitions), while the remaining acquire resistance over time (with disease progression at least 6 months after initiating ET for a/mBC (Menarini, 2023; Cogliati, et al., 2022; Gennari, et al., 2021; Belachew & Sewasew, 2021; Lei, Anurag, Haricharan, Gou, & Ellis, 2019; Patel, Klein, Tiersten, & Sparano, 2023; Rani, Stebbing, Giamas, & Murphy, 2019; Rasha, Sharma, & Pruitt, 2021; Xu, et al., 2021).

Several molecular mechanisms have been identified which underlie acquired endocrine resistance, including acquired mutations in specific genes (e.g., ESR1, the gene which encodes for ER α) (Chen, et al., 2022).

Mutation of the ESR1 gene is a key mechanism of acquired resistance to ET. ESR1 mutations alter the ligand-binding domain of ER, resulting in a ligand-independent, constitutively active receptor that enhances cancer growth, metastasis, and resistance (Brett, Spring, Bardia, & Wander, 2021; Chen, et al., 2022). This decreases the affinity of ER for estrogen, SERMs, and SERDs, however elacestrant as a SERD can still bind to the mutated ER. ESR1 mutations are rarely detected in

treatment-naïve primary tumours (Hartkopf, Grischke, & Brucker, 2020), and progression due to ESR1-mutation occurs more frequently with longer exposure to ET for a/mBC (Cogliati, et al., 2022; Brett, Spring, Bardia, & Wander, 2021; Jeselsohn, et al., 2018; Jeselsohn, et al., 2014; Schiavon, et al., 2015; Bidard, et al., 2022; Allouchery, et al., 2018). ESR1 mutations affect up to 40% of ER+ cases previously treated with ET in the metastatic setting (Brett, Spring, Bardia, & Wander, 2021; Santiago Novello, Lobo, Silveira Vilbert, Sanches, & Cesca, 2023).

Survival benefit in 2L+ treatment for ER+/HER2- a/mBC is limited and the treatment benefit diminishes with each line of therapy, with worse treatment responses associated with patients with ESR1-mut tumours (Turner, et al., 2020; Lindeman, et al., 2022; Bonotto, et al., 2015; Planchat, et al., 2011; Radius Pharmaceuticals Inc., 2022; Sledge, et al., 2020). Additionally, all 2L treatment options have limitations in treating patients with ER+/HER2- ESR1-mutation a/mBC, with limited efficacy and safety profiles and no robust efficacy evidence in patients with ESR1-mut tumours who have progressed on ET + CDK4/6i.

Provide a rationale for the specifics of the eligible population:

ER+/HER2- a/mBC is a devastating disease with poor treatment outcomes, which diminish with each line of therapy (Turner, et al., 2020; Lindeman, et al., 2022; Bonotto, et al., 2015; Planchat, et al., 2011; Radius Pharmaceuticals Inc., 2022; Sledge, et al., 2020). ESR1 mutations are acquired mutations associated with resistance to ET, and patients with a/mBC harboring these mutations have a poorer prognosis (Brett, Spring, Bardia, & Wander, 2021).

The duration of exposure to ET based regimens in the treatment of 1L ER+/HER2- a/mBC has increased due to the combination with CDK4/6i (the median PFS of ET+CDK4/6i treatment ranges from 9.5 to 28.1 months) (Piezzo, et al., 2020). Longer ET exposure (usually in combination with CDK4/6i) increases the chance of developing acquired resistance due to ESR1 mutation. Therefore, a novel patient population with ESR1-mutated tumours can be identified, with a high unmet need for effective new treatment options in 2L+, with well-tolerated and manageable AEs and that allow maintaining HRQoL (Turner, et al., 2020; Brett, Spring, Bardia, & Wander, 2021; Jeselsohn, et al., 2018; Jeselsohn, et al., 2014; Schiavon, et al., 2015; Bidard, et al., 2022; Allouchery, et al., 2018).

The ESMO metastatic breast cancer living guideline (ESMO, 2023b) provides a biomarker-based approach to 2L+ treatment, recommending treatment selection based on presence of PIK3CAm, ESR1 mutation and germline BRCA/PALB2m in patients with no imminent organ failure.

Currently, there are no reimbursed treatments that specifically target patients with ESR1-mutated tumours and existing treatments are associated with poor prognosis in this patient population (Turner, et al., 2020; Brett, Spring, Bardia, & Wander, 2021; Bidard, et al., 2022; Lindeman, et al., 2022).

Elacestrant is a next-generation endocrine treatment for patients with ER+/HER2- a/mBC with an activating ESR1 mutation, who have disease progression following at least one line of endocrine therapy including a CDK 4 /6 inhibitor.

In the EMERALD trial, the use of elacestrant significantly improved PFS in patients with ER+/HER2- a/mBC in the overall population and in patients with ESR1 mutations in ER+, a/mBC cancer who had disease progression during or after previous ET, with or without a CDK4/6 inhibitor, compared to treatment with standard of care (SOC) alone (Bardia, et al., 2019). Elacestrant significantly reduced the risk of progression or death by 45% vs SOC ET in patients with ESR1-mutated tumours (HR = 0.55; 95% CI, 0.39 to 0.77; P = 0.0005). Patients receiving elacestrant experienced a median PFS of

3.8 months vs 1.9 months with SOC (Bidard, et al., 2022). Patients with ESR1-mutated tumours that received ≥ 12 months of prior CDK4/6i, achieved a median PFS of 8.6 months with elacestrant vs 1.9 months with SOC ET (HR 0.410; 95% CI, 0.262 to 0.634) (Bardia A. , et al., 2023).

The EMERALD trial results highlighted this role of ESR1 mutational status using ctDNA extracted from blood (liquid biopsy) as a predictive biomarker and a tool to guide clinicians in innovative and personalised therapeutic decisions (Bidard, et al., 2022). Indeed, elacestrant is the first estrogen receptor antagonist showing efficacy in an ESR1 mutant population.

The proposed medical service is testing for ESR1 mutations using ctDNA extracted from blood (liquid biopsy) in patients with ER+/HER2- a/mBC who have disease progression following at least one line of ET including a CDK 4/6i, to determine eligibility for PBS-subsidised elacestrant.

Are there any prerequisite tests?

No

Are the prerequisite tests MBS funded?

No

Provide details to fund the prerequisite tests:

Elacestrant is for use in patients with ER+/HER2- a/mBC who have relapsed on ET. As stated above, one of the mechanisms of resistance to ET is the appearance of activating ESR1 missense mutations which can lead to unregulated signalling.

- i. The clinical evidence base for elacestrant, the pivotal EMERALD trial, utilised only a liquid biopsy as biological specimen to assess the presence of a ESR1 mutation in ctDNA (extracted from blood)
- ii. The biology of the tumour
 - a. ESR1 mutations often emerge at the time of first or subsequent progressions post ET/AI treatment (Brett, Spring, Bardia, & Wander, 2021) (Jeselsohn, et al., 2014)
 - b. The frequency of ESR1 mutations changes during the course of the disease (Cogliati, et al., 2022) (Brett, Spring, Bardia, & Wander, 2021) (Jeselsohn, et al., 2014) (Jeselsohn, et al., 2018) (Bidard, et al., 2022) (Allouchery, et al., 2018)
 - c. Liquid biopsy has been shown to be sensitive for identifying this mutation
 - d. Higher prevalence of actionable mutations is detected in liquid biopsy vs. tissue biopsy (Dustin, Gu, & Fuqua, 2019; Vidula, et al., 2021; Sivakumar, et al., 2022).
- iii. Archived tissue is not suitable for ESR1 mutational testing (Bardia, et al., 2022)
- iv. In addition to the predictive value of ESR1 mutations in ctDNA extracted from blood, the ease of use and timing of tests are to be considered. Indeed, repeated tests may be required (after 2L+ ET treatment) and multiple tissue biopsies are not practical and inconvenient for a patient.

Testing for these activating mutations is not currently routinely performed as there is no available drug to treat this population. Based on the clinical evidence base for elacestrant, the biology of the

tumour and the need for repeat testing, ctDNA extracted from blood is the preferred specimen to test for ESR1 mutations. Therefore, the proposed ESR1 mutational testing is conducted using ctDNA extracted from blood (liquid biopsy) and performed by a molecular pathologist and/or a registered anatomical pathologist in an accredited laboratory.

The proposed test – Testing for ESR1 mutations using ctDNA extracted from blood (liquid biopsy)

Using ESR1 mutations as a predictive biomarker for treatment with elacestrant optimises treatment outcomes and informs physicians about the potential clinical benefit in ER+/HER2- a/mBC patients (Bidard, et al., 2022).

The key phase III EMERALD trial has established that ESR1 mutations in blood is a predictive biomarker to guide clinicians in innovative and personalised therapeutic decisions with elacestrant. Longer exposure to ET (specifically to AI) increases the risk of developing acquired resistance due to ESR1 mutation. ESR1 mutation is unlikely to be detectable on diagnosis of early BC where this mutation is rare, and therefore testing for ESR1 mutations is relevant at each progression during the metastatic treatment course (Brett, Spring, Bardia, & Wander, 2021; Allouchery, et al., 2018).

An archived sample from a tissue biopsy at time of first diagnosis of BC is therefore not adequate. ctDNA extracted from blood (liquid biopsy) is required as a specimen after exposure to ET to determine the ESR1 mutational status, and is the only suitable specimen:

- i. The clinical evidence base for elacestrant, the pivotal EMERALD trial, utilised only a liquid biopsy as biological specimen to assess the presence of a ESR1 mutation in ctDNA (extracted from blood)
- ii. The biology of the tumour
 - a. ESR1 mutations often emerge at the time of first or subsequent progressions post ET/AI treatment (Brett, Spring, Bardia, & Wander, 2021) (Jeselsohn, et al., 2014)
 - b. The frequency of ESR1 mutations changes during the course of the disease (Cogliati, et al., 2022) (Brett, Spring, Bardia, & Wander, 2021) (Jeselsohn, et al., 2014) (Jeselsohn, et al., 2018) (Bidard, et al., 2022) (Allouchery, et al., 2018)
 - c. Liquid biopsy has been shown to be sensitive for identifying these mutations
 - d. Higher prevalence of actionable mutations is detected in liquid biopsy vs. tissue biopsy (Dustin, Gu, & Fuqua, 2019; Vidula, et al., 2021; Sivakumar, et al., 2022).
- iii. Archived tissue is not suitable for ESR1 mutational testing (Bardia, et al., 2022)
- iv. In addition to the predictive value of ESR1 mutations in ctDNA extracted from blood, the ease of use and timing of tests are to be considered. Indeed, repeated tests may be required (after 2nd line or 3rd line ET treatment) and multiple tissue biopsies are not practical and inconvenient for a patient.
 - a. testing for ESR1 mutations should occur at each progression during a/mBC treatment course if not detected previously.

(Jeselsohn, et al., 2014; Jeselsohn, et al., 2018; Allouchery, et al., 2018; Schiavon, et al., 2015; Brett, Spring, Bardia, & Wander, 2021; Burstein, DeMichele, Somerfield, & Henry, 2023),

Table 1 Requested new MBS item descriptor

Category 6 – Pathology Services		
MBS item XXXX	Group P7 – Genetics	
<p>A test of ctDNA extracted from blood plasma for the detection of ESR1 activating mutations in an altered tumour, in a patient with:</p> <ul style="list-style-type: none"> 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. <p>As requested by a specialist or consultant physician, to determine eligibility for treatment with elacestrant under the Pharmaceutical Benefits Scheme (PBS)</p>		
Fee: \$XX	Benefit: 75% = \$XX	85% = \$XX

Intervention

Name of the proposed health technology:

Test: Testing for ESR1 mutations in ctDNA extracted from blood (liquid biopsy) to determine eligibility for treatment with elacestrant, a selective estrogen receptor degrader (SERD) to inhibit ER signalling.

In the EMERALD clinical trial, the Guardant360® CDx test (liquid biopsy) was used to identify patients harbouring ESR1-mutations following progression on ET. The Guardant360® CDx uses NGS and high throughput hybridisation-based capture technology to detect single nucleotide variants (SNVs), insertions and deletions (indels), copy number amplifications (CNAs) and fusions in a targeted panel of 55 genes. This includes full coverage of the ESR1 gene, encompassing missense mutations in the ligand-binding domain.

The Guardant360® CDx is not available in Australia and is proposed as the reference standard for the submission.

Next-generation sequencing (NGS) or digital droplet PCR (ddPCR) techniques can be utilised for ESR1 mutational testing. In EMERALD, ESR1 mutations in liquid biopsy were assessed using an NGS method

NGS assays including the ESR1 gene cover the full ligand binding domain of the ESR1 gene where the missense mutations of interest are located. The availability of various commercial NGS assays offers pathologists a ready-to-use solution which can minimise the level of technical failure and can easily be implemented in a laboratory. Moreover, NGS technology is now an established technology in Australia.

There is a lack of commercially available ddPCR-based assays for ESR1 mutations. A laboratory would need to assemble its own ddPCR assay. Such an assay would only detect a defined number of mutations (essentially hotspot mutations). As such, ddPCR may present some challenges with regard to ease of use and implementation and utilization in routine clinical practice.

The applicant continues to engage with local laboratories and experts to understand the utilisation of these methods in the context of this codependent submission.

Drug: Orserdu (elacestrant)

Elacestrant is a next generation, potent, selective and orally active estrogen receptor antagonist and degrader that acts by binding and targeting the ER for degradation, thus limiting ER-induced tumour growth (FDA, 2023; EMA, 2023). In contrast to fulvestrant, elacestrant has oral bioavailability and can be administered as a single daily tablet (FDA, 2023; EMA, 2023). Elacestrant provides an innovative 2L+ treatment for patients with ER+/HER2- a/mBC with tumours with activating ESR1-mutations.

Elacestrant is currently undergoing TGA evaluation for treatment in this population.

Describe the key components and clinical steps involved in delivering the proposed health technology:

The proposed test involves identification of ESR1 mutations using ctDNA extracted from blood (liquid biopsy) from patients with HR+/HER2- a/mBC. NGS or ddPCR techniques can be utilised for ESR1 mutational testing and it is understood that NGS is the preferred technique.

NGS enables the identification of hundreds of genes at one time. Using NGS the pathologist will be able to preselect the genes to identify - often referred to as 'A Testing Panel'. In this case, a panel will be used to identify ESR1 mutations and potentially also PIK3CA, or others.

Identify how the proposed technology achieves the intended patient outcomes:

The application requests MBS funding for testing to identify activating ESR1 mutations in patients with ER+/HER2- a/mBC, who have disease progression following at least one line of ET, including a CDK 4/6i, to determine PBS eligibility for elacestrant.

In the pivotal trial, EMERALD, elacestrant significantly reduced the risk of progression or death by 45% vs SOC ET in patients with ESR1-mutated tumours (HR = 0.55; 95% CI, 0.39 to 0.77; P = 0.0005). Patients receiving elacestrant experienced a median PFS of 3.8 months vs 1.9 months with SOC (Bidard, et al., 2022).³⁴ Patients with ESR1-mutated tumours that received ≥ 12 months of prior CDK4/6i, achieved a median PFS of 8.6 months with elacestrant vs 1.9 months with SOC ET (HR 0.410; 95% CI, 0.262 to 0.634) (Bardia A. , et al., 2023). Elacestrant had a well-tolerated and manageable safety profile, with a low discontinuation rate.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

No

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

N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

No

Provide details and explain:

In Australia, Menarini is 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, Menarini has initiated pivotal activities to prepare for the future commercial availability of elacestrant:

- Building infrastructure and ensuring technical readiness for ESR1 mutation liquid biopsy testing
- Implementing an External Quality Program (EQA) for ESR1 mutation testing in liquid biopsy
- Raising awareness about ESR1 mutation testing in liquid biopsy

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Oncologists who assess eligibility of patients for ESR1 mutational 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 a registered anatomical pathologist are responsible for conducting the detection, diagnosis and reporting of the pathology result to help guide and determine treatment.

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

N/A

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

A registered anatomical pathologist is responsible for conducting the detection, diagnosis and reporting of the pathology results which guide and determine treatment. A specialist (medical oncologist, breast surgeon, interventional radiologist) provides the specimen and a test request form for testing.

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

Yes

Provide details and explain:

Training and qualifications for laboratory personnel performing the testing of ESR1 mutations by NGS or dPCR would be the same as those required for laboratory personnel currently performing other cancer biomarker genomic testing.

Pathology laboratories performing NGS or dPCR testing would need to be NATA-accredited, and as per other cancer biomarker genomic tests, competence in ESR1 mutation testing would be monitored via a Quality Assurance Program (QAP) by the Royal College of Pathologists of Australia (RCPA). Often RCPA cooperates with QAP providers in Europe and Australian labs are included in their programs. Menarini-Stemline is currently supporting similar QAPs for ESR1 mutational testing

in Europe with appropriate proficiency testing organizations. Contact with RCPA has been initiated to discuss details of a potential QAP in Australia.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

(Select all relevant settings)

- Consulting rooms
- Day surgery centre
- Emergency Department
- Inpatient private hospital
- Inpatient public hospital
- Laboratory
- Outpatient clinic
- Patient's home
- Point of care testing
- Residential aged care facility
- Other (please specify)

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

Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:

N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian healthcare system). This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:

Test: The nominated comparator is no test.

Testing for ESR1 mutation is not currently funded for BC patients, therefore the comparator is no test.

In the recently updated NCCN guidelines, the panel has included elacestrant as a new treatment option for postmenopausal females or adult males with ER-positive, HER2-negative, ESR1-mutated tumours after disease progression on 1 or 2 prior lines of ET, including 1 line containing a CDK4/6 inhibitor (Gradishar, et al., 2023). The panel recommends evaluating ESR1 mutational status using next-generation sequencing or by assessing the ctDNA in the blood using NGS or PCR. Because ESR1 mutations are acquired during treatment, primary archived BC should not be used as a source of tumour tissue for ESR1 mutation testing.

Table 2 Biomarkers associated with FDA-approved therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2- negative	PIK3CA activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2- negative ¹	ESR1 mutation	NGS, PCR (blood)	Elacestrant	Category 2A	Other recommended regimen
Any	NTRK fusion	FISH, NGS, PCR (tissue block)	Larotrectinib Entrectinib	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR (tissue block)	Pembrolizumab Dostarlimab-gxly	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab	Category 2A	
Any	RET-fusion	NGS	Selpercatinib	Category 2A	

1. For postmenopausal females or adult males with ER-positive, HER2-negative, ESR1-mutated disease after progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor.

Source: Adapted from NCCN Guidelines 2023

Drug: The comparator is standard of care (SOC) 2L+ treatment, including ET (the definition of SOC will be refined for the submission based on local clinical practice).

List any existing MBS item numbers that are relevant for the nominated comparators:

N/A

Provide a rationale for why this is a comparator:

N/A

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

(Please select your response)

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

Outline and explain the extent to which the current comparator is expected to be substituted:

The nominated comparator is no test.

Outcomes

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

(Please select your response)

- Health benefits
- Health harms
- Resources
- Value of knowing

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

The EMERALD trial was a multinational, open-label, randomised study comparing the efficacy and safety of elacestrant with SOC ET (fulvestrant or AI) in patients with ER+/HER2- a/mBC previously treated with one or two lines of ET, including a CDK4/6i (Bidard, et al., 2022). In the EMERALD trial, elacestrant demonstrated a statistically significant and clinically meaningful 45% reduction in the risk of progression or death vs. SOC endocrine monotherapy (HR: 0.55; 95% CI: 0.39, 0.77, p=0.0005; median PFS: 3.8 months vs. 1.9 months) in patients with ESR1-mutated tumours (Bidard, et al., 2022).

Elacestrant demonstrated long and sustained patient benefit, with 26.8% patients free of progression at 12 months vs. 8.2% in the SOC arm, a 3-fold increment in the rates of patients alive or free of progression at one year for elacestrant-treated patients vs patients treated with SOC. An absolute increase of 6.7 months in median PFS vs SOC (8.6 months vs.1.9 months) in endocrine sensitive patients with prior CDK4/6i exposure of at least 12 months (71.6% of patients harbouring ESR1-mut tumours in the EMERALD trial) (Kaklamani, et al., 2023; Bardia, et al., 2022; Varella & Cristofanilli, 2023).

Testing for ESR1 mutations in ctDNA extracted from blood (liquid biopsy) is expected to lead to a change in clinical management as patients with a positive result may be eligible to receive treatment with elacestrant. This change is expected to lead to a significant improvement in clinical outcomes, as demonstrated by the pivotal EMERALD trial.

Test outcomes:

Sensitivity, specificity, positivity predictive value (PPV), negative predictive value (NPV).

Treatment outcomes:

- Progression-free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR), Complete response (CR), partial response (PR), stable disease (SD)
- Duration of response (DR)
- Safety, tolerability

Health care system:

- Cost effectiveness of testing and treatment, financial implications

Proposed MBS items

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

Currently, any testing for ESR1 mutations in ctDNA extracted from blood is self-funded by patients.

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

MBS item number	N/A
Category number	Category 6 – Pathology Services
Category description	Group P7 – Genetics
Proposed item descriptor	<p>A test of ctDNA extracted from blood plasma for the detection of ESR1 missense mutations in an altered tumour, in a patient with:</p> <ul style="list-style-type: none"> 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. <p>As requested by a specialist or consultant physician, to determine eligibility for treatment with elacestrant under the Pharmaceutical Benefits Scheme (PBS)</p>
Proposed MBS fee	The proposed MBS fee is currently unavailable
Indicate the overall cost per patient of providing the proposed health technology	A detailed utilisation analysis will be presented in the integrated co-dependent MSAC/PBAC submission.
Please specify any anticipated out of pocket expenses	A detailed utilisation analysis will be presented in the integrated co-dependent MSAC/PBAC submission.
Provide any further details and explain	A detailed utilisation analysis will be presented in the integrated co-dependent MSAC/PBAC submission.

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

A clinical management algorithm is provided below.

Prior to being eligible for the proposed health technology, patients will have been diagnosed with ER-positive, HER2-negative, a/mBC and have experienced disease progression following at least one line of endocrine therapy (ET), including a CDK 4/6 inhibitor.

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

No.

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

The only difference in the management is the requirement of a blood draw from patients to assess the presence of ESR1 mutations, as compared to the comparator health technology.

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

The key components and clinical steps involved in delivering a ctDNA extracted from blood plasma (liquid biopsy) genetic mutation test in patients with HR-positive/HER2-negative breast cancer are as follows:

- Oncologists who assess eligibility of patients for ESR1 mutational 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. Sample collection is non-invasive and rapid.
- A registered molecular pathologist and a registered anatomical pathologist are responsible for conducting the detection, diagnosis and reporting of the pathology result in a NATA accredited laboratory using NGS or dPCR to help guide and determine treatment.

If the presence of ESR1 activating mutations is confirmed in ctDNA extracted from blood, the patient may be eligible for PBS-subsidised treatment with elacestrant.

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

The current comparator is no test. Patients would receive SOC 2L+ treatments, predominantly accessed via the PBS.

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

Currently, there are no treatments that specifically target patients with ESR1 activating mutation tumours and as such, no testing for this mutation occurs as part of routine clinical practice.

With the availability of ctDNA extracted from blood plasma (liquid biopsy) ESR1 mutation testing, patients with confirmed ESR1 activating mutations may be eligible for PBS-reimbursed elacestrant treatment.

Using ESR1 mutations as a predictive biomarker for the benefit of elacestrant optimises treatment outcomes. This may create healthcare system efficiencies, in terms of costs and resource allocation.

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

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

With the availability of ctDNA extracted from blood plasma (liquid biopsy) ESR1 mutation testing, patients with confirmed ESR1 activating mutations may be eligible for PBS-reimbursed elacestrant treatment.

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

An ESR1 mutation may emerge at each progression, therefore testing for ESR1 mutations would be relevant at each progression during the metastatic treatment course (if not detected earlier).

If the presence of ESR1 activating mutations is confirmed in ctDNA extracted from blood, the patient may be eligible for PBS-subsidised treatment with elacestrant.

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

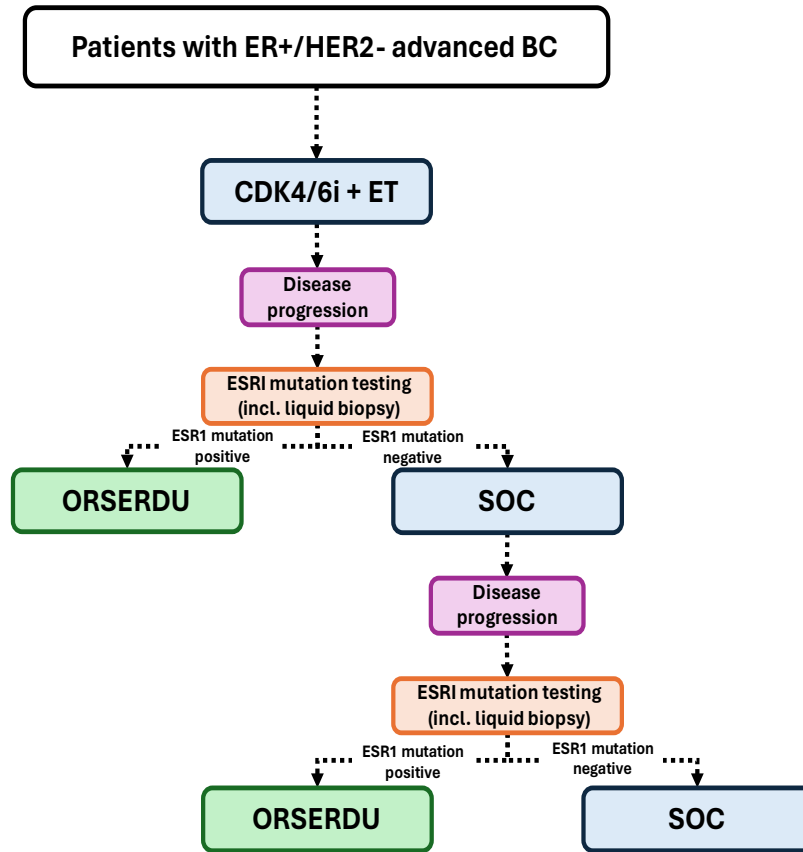
As demonstrated in the clinical algorithm below, there are a number of treatment options available in the 2L+ setting. Patients may subsequently move between these treatment options for later lines of therapy, including moving to best supportive care.

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

A clinical management algorithm is provided below. Guideline recommended treatment options available in the 2L+ setting include fulvestrant monotherapy, everolimus + exemestane, switch ET, and chemotherapy. For patients with imminent organ failure/visceral crisis, chemotherapy is generally recommended.

SOC (informed by international guidelines) is to be validated with local clinicians.

Figure 1: Clinical management algorithm



Abbreviations: BC = breast cancer, ChT = chemotherapy, ER+/HER2- = estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative; ESR1 = estrogen receptor 1; ET = endocrine therapy; SOC = standard of care

Claims

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

(Please select your response)

- Superior
- Non-inferior
- Inferior

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

Based on the results of the pivotal trial, EMERALD, testing for ESR1 mutations in ctDNA extracted from blood (liquid biopsy) + elacestrant is superior to no testing + SOC 2L+ treatment, including ET.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

Due to the acquisition of mutations in ESR1 as a result of longer exposure to ET (specifically, to AI) in combination with CDK4/6i, a new patient population can be identified that is in urgent need of a treatment with superior efficacy, a well-tolerated and manageable safety profile that allows to maintain HRQoL compared to the current 2L+ options (Brett, Spring, Bardia, & Wander, 2021; Jeselsohn, et al., 2018; Jeselsohn, et al., 2014; Schiavon, et al., 2015; Bidard, et al., 2022; Allouchery, et al., 2018).

Elacestrant is the first biomarker-driven endocrine treatment for patients with ER+/HER2- ESR1-mutation a/mBC with who have progressed following at least one line of ET + CDK4/6i and fills the unmet need of patients with ESR1- mutation tumours (Bidard, et al., 2022).

Identify how the proposed technology achieves the intended patient outcomes:

In the EMERALD trial, elacestrant significantly reduced the risk of progression or death by 45% vs SOC ET in patients with ESR1-mutated tumours (HR = 0.55; 95% CI, 0.39 to 0.77; P = 0.0005). Patients receiving elacestrant experienced a median PFS of 3.8 months vs 1.9 months with SOC (Bidard, et al., 2022). Patients with ESR1-mutated tumours that received ≥ 12 months of prior CDK4/6i, achieved a median PFS of 8.6 months with elacestrant vs 1.9 months with SOC ET (HR 0.410; 95% CI, 0.262 to 0.634) (Bardia A. , et al., 2023).

Elacestrant demonstrated long and sustained patient benefit, with 26.8% patients free of progression at 12 months vs. 8.2% in the SOC arm, a 3-fold increment in the rates of patients alive or free of progression at one year for elacestrant-treated patients vs patients treated with SOC. An absolute increase of 6.7 months in median PFS vs SOC (8.6 months vs.1.9 months) in endocrine sensitive patients with prior CDK4/6i exposure of at least 12 months (71.6% of patients harbouring ESR1-mutated tumours in the EMERALD trial) (Kaklamani, et al., 2023; Bardia, et al., 2022; Varella & Cristofanilli, 2023).

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

(Please answer either Yes or No, deleting text as required)

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits? No

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

N/A

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

(Please select your response)

- More costly
- Same cost
- Less costly

Provide a brief rationale for the claim:

The PBS listing of elacestrant will result in the utilisation of liquid biopsy for the testing of ESR1 mutations.

Overall, the listing of testing for ESR1 mutations in ctDNA extracted from blood (liquid biopsy) and elacestrant on the MBS and PBS, respectively, is expected to be more costly than no testing + SOC 2L+ treatment, including ET.

Summary of Evidence

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

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	Review	ESR1 gene mutations and liquid biopsy in ER-positive breast cancers: a small step forward, a giant leap for personalization of endocrine therapy	Technically, several options exist, including Next Generation Sequencing and ultra-sensitive PCR-based techniques. In this context, personalization of ET through the surveillance of ESR1 mutations in the plasma of HR+ BC patients throughout the disease course represents an innovative way to improve the standard of care.	Betz M. et al. Cancers 2023; 15: 5169 https://doi.org/10.3390/cancers15215	2023
2.	Phase III open-label, prospective randomized	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	Elacestrant is the first oral selective ER degrader demonstrating a significant PFS improvement versus SOC both in the overall population and in patients with ESR1 mutations with manageable safety in a phase III trial for patients with ER-positive/HER2-negative advanced breast cancer. Acquired ESR1 missense mutations are a predictive biomarker for the use Elacestrant in advanced ER+, HER2- breast cancer patients	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; 40: 3246-3256 Bidard FC. et al. JCO 2022; 40: 3246-3256 https://doi:10.1200/JCO.22.00338	2022

MSAC Application 1782 - Genetic testing to detect estrogen receptor 1 (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

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3.	Phase III open-label, prospective randomized	Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial	Trial showed that the early therapeutic targeting of ESR1 mutations detected in blood results in significant clinical benefit	Bidard FC. et al. Lancet Oncol. 2022; 23: 1367-1377 https://doi.org/10.1016/S1470-2045(22)00555-1	2022
4.	Phase I/II open-label, multicenter single-arm	Phase I/II Trial of Exemestane, Ribociclib, and Everolimus Women with HR+/HER2_ Advanced Breast Cancer after Progression on CDK4/6 Inhibitors (TRINITI-1)	ESR1 mutations were amongst the most common mutations at baseline. Patients with wildtype ESR1 at baseline had a numerically longer median PFS than patients who had mutated ESR1	Bardia J. et al. JCO 2021; 39: 1360-1370 https://doi:10.1158/1078-0432.CCR-20-2114	2021
5.	Phase II, double blind, prospective, randomised	Phase II trial of endocrine therapy with or without ribociclib after progression on CDK 4/6 inhibition in HR-positive, HER 2-negative metastatic breast cancer.	There was a statistically significant PFS improvement for patients randomly assigned to switched ET plus ribociclib (median, 5.29 months; 95% CI, 3.02 to 8.12 months) versus switched ET plus placebo (median, 2.76 months; 95% CI, 2.66 to 3.25 months) HR, 0.57 (95% CI, 0.39 to 0.85); $P = .006$. At 6 and 12 months, the PFS rate was 41.2% and 24.6% with ribociclib, respectively, compared with 23.9% and 7.4% with placebo.	Kalinsky K et al. 2023. Journal of Clinical Oncology, 41 (24): 4004-4013. https://pubmed.ncbi.nlm.nih.gov/37207300/	2023

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
6.	Phase II, prospective, randomised, multicentre	A randomized phase II study of fulvestrant, palbociclib, and avelumab after progression on CDK 4/6 inhibitor and aromatase inhibitor for HR-positive/HER2-negative metastatic breast cancer	The addition of palbociclib to fulvestrant did not improve PFS versus fulvestrant alone among patients with hormone receptor-positive/HER2- MBC whose disease had progressed on a previous CDK4/6i plus AI. The increased PFS seen with the addition of avelumab warrants further investigation in this patient population.	Mayer EL et al. J. Clin. Oncol. March 21, 2024. https://ascopubs.org/doi/abs/10.1200/JCO.23.01940	2024
5.	Review	ESR1 mutations as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer	ESR1-MUT arises in patients who receive AI in the metastatic setting, and this causes resistance to AI monotherapy, with cfDNA detection of ESR1-MUT preceding radiologic progression by 3-7 months	Brett O. et al. Breast Cancer Res. 2021; 23: 85 https://doi.org/10.1186/s13058-021-01462-3	2021
6.	Real-world clinical data study	Real-world clinical-genomic data identifies the ESR1 clonal and subclonal circulating tumor DNA (ctDNA) landscape and provides insight into clinical outcomes	Uniquely well-characterized clinical-genomic data in a proprietary dataset identified that approx. 30% of patients with advanced breast cancer had somatic ESR1 mutations following AI therapy, consistent with previously published data. The majority of patients had multiple subclonal ESR1 resistance mutations following AI treatment.	Hanna D. et al. Cancer Res. 2021; 81(Suppl. 4), PS18-15 https://doi.org/10.1158/1538-7445.SABCS20-PS18-15	2021
7.	Prospective-retrospective analysis from archived baseline plasma samples	Plasma ESR1 mutations and the treatment of estrogen receptor-positive advanced breast cancer	ESR1 mutation analysis in plasma after progression after prior AI therapy may help direct choice of further endocrine-based therapy	Fribbens C. et al. JCO 2016; 34: 2961-2968 https://pubmed.ncbi.nlm.nih.gov/27269946/	2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
8.	Meta-analysis	Clinical value of circulating ESR1 mutations for patients with metastatic breast cancer: a meta-analysis	The meta-analysis indicated that plasma ESR1 mutation assessment has prognostic significance and clinical value in guiding further endocrine therapy choice in ER+ MBC patients who received prior AI therapy.	Zhang K. et al. Cancer Management and Res. 2018; 10: 2573-2580 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6097501/	2018

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

*** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).

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

None identified.

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