MSAC Application 1783

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

Applicant: Roche Products 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 *PIK3CA* variants in patients with HR+/HER2-, locally advanced or metastatic breast cancer.

Component	Description
Population	**Test population** Adults with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) locally advanced or metastatic breast cancer, whose disease progressed during adjuvant endocrine therapy or within 12 months of completing adjuvant endocrine therapy. **Treatment population** Patients in the test population with one or more *PIK3CA* variants, for first line treatment with inavolisib.
Prior tests	• Tests required to confirm diagnosis of breast cancer (i.e. biopsy). • 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: oestrogen receptor (ER), progesterone receptor (PR) to define HR status, and HER2 status.
Intervention	**Test**: Circulating tumour DNA (ctDNA) or tumour tissue testing using Next Generation Sequencing (NGS) to characterise *PIK3CA* variants. **Treatment**: Inavolisib + palbociclib + fulvestrant for patients found to have one or more *PIK3CA* variants.
Comparator/s	**Test comparator**: No genetic testing for *PIK3CA* genetic variation **Treatment comparator:** Current standard of care. Endocrine therapy with or without CDK4/6 inhibitor is the current standard of care. Palbociclib + fulvestrant (which is a CDK4/6 inhibitor and endocrine therapy, respectively) was nominated as the comparator by the applicant, as per the INAVO120 trial.
Reference standard	No reference standard available for *PIK3CA* genetic variation testing in Australia.
Clinical utility standard	FoundationOne® Liquid CDx was the clinical utility standard as it was the most frequently used method in the INAVO120 trial.

Component	Description

Outcomes	***Test outcomes***
	Efficacy/effectiveness
	• Analytical performance, diagnostic and predictive accuracy of the proposed *PIK3CA* variants testing using NGS (sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)).
	• Comparison of the analytical performance (concordance and discordance) of the proposed *PIK3CA* variants testing using NGS (for both ctDNA and tumour tissue) to the clinical utility standard (no reference standard).
	• Comparison of *PIK3CA* variants tests using NGS (commercial and in-house developed), that are likely to be used in Australia, considering both ctDNA and tumour tissue testing.
	• Comparative diagnostic accuracy between ctDNA from blood sample and tumour tissue sample (fresh/archival/primary/metastasis sample) in the identification of *PIK3CA* variants.
	• Clinical validity of test:
	  ○ Differential prognostic effect of the proposed *PIK3CA* variants testing in locally advanced or metastatic breast cancer (LA/mBC), particularly including an assessment of whether this prognostic effect varies further according to whether the patient is positive or negative for *PIK3CA* variants.
	• Clinical utility of test:
	  ○ Treatment effect modification of inavolisib as a consequence of *PIK3CA* status from testing using ctDNA or tumour tissue sample
	• Other test related considerations:
	  ○ Test turnaround time.
	  ○ Test failure rates and re-biopsy rates (if tumour tissue sample).
	Safety outcomes
	• Adverse events associated with collection of plasma sample for ctDNA analysis, biopsy for tumour tissue testing, and re-biopsy (e.g. for patients with an inadequate tissue sample for tumour testing).
	Healthcare resources
	• Estimated number of patients to be tested.
	• Cost of test intervention and associated delivery cost.
	• Cost of blood plasma collection.
	• Cost of re-biopsy (if tumour tissue sample).
	• Cost of re-test (i.e. the cost of tumour tissue testing if this is conducted after a negative ctDNA test).
	Treatment outcomes
	Efficacy/effectiveness
	• Progression free survival.
	• Overall survival.
	• Response rate.

Component	Description
	• Quality of life. • Comparative effectiveness of treatment based on tumour and ctDNA variant status. *Safety Outcomes* • Comparative safety and tolerability of inavolisib (in combination with palbociclib + fulvestrant), compared to alternative first line treatments in patients with/without *PIK3CA* variants, assessed by adverse events, discontinuation rates, deaths and collection of clinical chemistry/haematology parameters. *Healthcare resources* • Cost of treatment intervention. *Total Australian Government Healthcare costs* • Total cost to the Medicare Benefits Schedule (MBS). • Total cost to the Pharmaceutical Benefits Scheme (PBS). • Total cost to other healthcare services.
Assessment questions	What is the safety, effectiveness, cost-effectiveness and total costs of a genetic test to detect *PIK3CA* variants and treatment with inavolisib (in combination with palbociclib + fulvestrant), versus no testing and treatment with an alternative first line treatment, in a patient with HR+/HER2- LA/mBC? Does testing for *PIK3CA* variants predict a treatment effect modification with inavolisib (in combination with palbociclib + fulvestrant)?

Purpose of application

The codependent application was received by the Department of Health and Aged Care from Roche Products Pty Ltd, and requested:

- Medicare Benefits Schedule (MBS) listing of genetic testing to detect *PIK3CA* variants for the determination of patient eligibility for treatment; and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of inavolisib, in addition to palbociclib and fulvestrant, for the treatment of hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) locally advanced (LA) or metastatic breast cancer (mBC), in patients whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy (ET).

The applicant's overall claim is that *PIK3CA* testing followed by inavolisib in combination with palbociclib and fulvestrant in patients with detected *PIK3CA* variants is superior to no *PIK3CA* testing and treatment with palbociclib plus fulvestrant.

Based on the INAVO120 trial primary analysis, patients with detected *PIK3CA* variants and treated with inavolisib + palbociclib + fulvestrant experienced significant improvement in progression free survival (PFS) with a stratified hazard ratio (HR) of 0.43 (95% CI: 0.32-0.59), and an interim analysis of overall survival (OS) with a stratified HR of 0.64 (95% CI: 0.43-0.97), compared to the control group (placebo + palbociclib + fulvestrant) (Jhaveri KL et al 2023). All patients enrolled in the INAVO120 trial were assessed for having *PIK3CA* variants by testing of circulating tumour deoxyribonucleic acid (ctDNA) or tumour tissue sample. It was noted that grade 3-5 adverse events were more frequent in the treatment group (92% in the treatment group vs 83.3% in the control group). However, the results of INAVO120 have not yet been published in a peer reviewed journal. Communication received from the applicant at the pre-PASC stage stated that the manuscript reporting the results of the INAVO120 trial had been submitted to a journal with publication anticipated in the third quarter of 2024.

Inavolisib was granted Priority Review by the United States Food and Drug Administration (US FDA) and the target action date for FDA's decision is 27 November 2024 (Genentech 2024). Inavolisib is also currently under accelerated assessment by the European Medicines Agency (EMA 2024). The applicant advised that the Therapeutic Goods Administration (TGA) has accepted the Australian inavolisib dossier for evaluation under the Project Orbis collaborative regulatory pathway. The TGA decision is expected in May 2025, and if successful, registration on the Australian Register of Therapeutic Goods (ARTG) is expected in June 2025.

The proposed therapeutic indication of inavolisib to the TGA was:

- [TRADENAME], in combination with palbociclib and endocrine therapy, is indicated for the treatment of adult patients with *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or after adjuvant therapy or progression on an endocrine-based regimen in the metastatic setting.

- Patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer should be selected for treatment with [TRADENAME] based on the presence of one or more *PIK3CA* mutations using a validated assay. *PIK3CA* mutation status should be established prior to initiation of [TRADENAME] therapy.

The applicant stated that the proposed TGA indication for inavolisib was currently aligned with the submission to the FDA, but it may be subject to amendment throughout the assessment period depending on the TGA's final decision on the population.

There are several other MSAC applications related to *PIK3CA* testing, ctDNA testing, and/or the same target population:

- MSAC application 1604 (considered by PASC at its December 2019 meeting) - *PIK3CA* mutation testing in postmenopausal women or men with advanced breast cancer who have progressed during or following treatment with an aromatase inhibitor. This application did not progress to the assessment phase.
- MSAC application 1766 (considered by PASC at its April 2024 meeting) – Genetic testing to detect AKT-pathway alterations (*PIK3CA, PTEN* and *AKT1*) in patients with HR+/HER2- advanced breast cancer, to determine eligibility for PBS subsidised capivasertib treatment. This application has progressed to the assessment phase and is due for consideration by MSAC in November 2024.
- MSAC application 1782 (considered by PASC at its August 2024 meeting) - Genetic testing to detect estrogen receptor 1 mutations in patients with estrogen receptor positive, HER2-negative, locally advanced or metastatic breast cancer, to determine eligibility for treatment with PBS subsidised elacestrant.

PICO criteria

Population

The applicant's proposed test population is patients with HR+/HER2- LA/mBC, based on the communication provided during the pre-PASC stage. The HER2- subtype includes HER2 with an immunohistochemistry (IHC) score of 0 and 1+, or an IHC score of 2+ accompanied by a negative in situ hybridisation (ISH) test. The proposed treatment population is the test population with one or more *PIK3CA* variants, who had disease progression during adjuvant therapy or within 12 months of adjuvant therapy, for treatment with inavolisib, in addition to palbociclib and fulvestrant.

Referring to the INAVO120 study design, the study population included HR+/HER2- LA/mBC patients with *PIK3CA* variants and disease progression during or within 12 months of adjuvant ET completion (Jhaveri et al. 2023; Juric et al. 2024). Treatment with inavolisib + palbociclib + fulvestrant was positioned as first-line (1L) therapy in HR+/HER2- LA/mBC with *PIK3CA* variants. The applicant's proposed test population was broader than the study population in the INAVO120 trial, suggesting all patients with HR+/HER2- LA/mBC would be eligible for *PIK3CA* variants testing (i.e. without applying the restriction that a patient had progressed during or within 12 months of adjuvant ET completion). This discrepancy between the proposed test population and the population in the key clinical trial may mean that the clinical outcomes

reported in the INAVO120 trial may not be generalisable to the proposed test population. Notably, the population remains uncertain given that inavolisib is not yet approved by the US FDA or TGA. The applicant advised that the proposed population will be refined and aligned to the populations approved by the US FDA and Australian TGA, once this information is available.

PASC's advice regarding the most appropriate test population was requested, i.e. whether or not the test population should include the restriction to patients whose disease progressed during treatment or within 12 months of completing adjuvant ET (as in the INAVO120 trial).

PASC noted that the INAVO120 study population (those randomised to receive inavolisib or the comparator treatment) were patients with HR+/HER2- LA/mBC with one or more PIK3CA *variant(s), with disease progression during or within 12 months of adjuvant ET completion.*

PASC noted that the test population proposed in the pre-PASC PICO was restricted to patients 'following recurrence or progression on or after adjuvant ET' and noted that the applicant proposed that this restriction be removed. PASC noted that there are arguments for and against PIK3CA *testing at BC diagnosis vs. at LA/mBC disease stage following progression on or after adjuvant ET when inavolisib is intended for use. PASC noted the applicant's concern that this restriction could prevent efficient use of tumour tissue, because it would mean that* PIK3CA *testing cannot be performed at the same time as testing for HR/HER2 status. The applicant noted that this restriction may prevent clinicians from obtaining the best possible understanding of the tumour biology in the early course of disease and would delay treatment initiation with inavolisib in eligible patients, given the laboratory turnaround time for* PIK3CA *testing may be delayed. In arguments in support of the restriction, PASC considered that scarcity of tumour tissue is generally not a concern for breast cancer compared with that for many other cancers (e.g. cholangiocarcinoma) and considered that testing at the time of treatment rather than diagnosis may address concerns of change in tumour* PIK3CA *status over time. PASC also considered that testing a broader population at diagnosis will likely lead to significant redundancy and costs associated with testing that has no influence on subsequent management. Taking all these issues into consideration, PASC advised that the test population should be patients with HR+/HER2- LA/mBC who have relapsed during or after adjuvant ET, so that the test can inform treatment decisions at the stage when inavolisib is intended for use.*

Background

Breast cancer (BC) is one of the most common cancer diagnoses in Australia (AIHW 2023). Between 1982 and the end of 2018, 253,623 people had been diagnosed with BC (AIHW 2023). About 20-30% of patients with early-stage BC will experience disease recurrence with distant metastases (Carson and Dear 2019; Peto et al. 2012). The Australian Institute of Health and Welfare (AIHW) further estimated 20,771 people will be diagnosed with BC in 2024, with an annual increase of ~2% in the long-term incidence projection for BC (AIHW 2023). Based on the incidence of BC reported in Australia in 2011, approximately 16.7% of patients were diagnosed with LA BC (stage III) or mBC (stage IV), and mortality rates increased in later stages of BC, older patients, and with time since diagnosis (AIHW 2023). The 5-year relative survival rate for mBC was 32%, as compared to >95% for stage I and II BC (AIHW 2023).

HR+/HER2- is the most common subtype, accounting for 78% of mBC cases, based on the Australian Metastatic Breast Circulating Biomarker study (Bujak et al. 2020). While ET is the standard therapy in the management of HR+ BC, about 15-40% of patients with BC develop resistance to ET (Haque and Desai 2019; Lei et al. 2019; Murphy and Dickler 2016; Schagerholm et al. 2024). Mechanisms of endocrine

resistance include abnormalities in the oestrogen/progesterone pathway, *ESR1* gene variants and alterations in the PI3K/AKT signalling pathway (Hartkopf et al. 2020).

Phosphatidylinositol 3-Kinase (PI3K) Pathway

The PI3K pathway has a central role in the PI3K/AKT/mTOR pathway, which regulates intracellular signalling processes such as cell proliferation, growth and metabolism (Paplomata and O'Regan 2014). PI3Kα, consisting of a p110α catalytic subunit and a p85α regulatory subunit, receives upstream activation signals from the receptor tyrosine kinases (RTK), and results in the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3) (Vasan et al. 2019). The accumulation of PIP3 at the plasma membrane activates protein kinase B (AKT), which stimulates downstream cascade effects of cell growth, proliferation, metabolism and survival (Vasan et al. 2019).

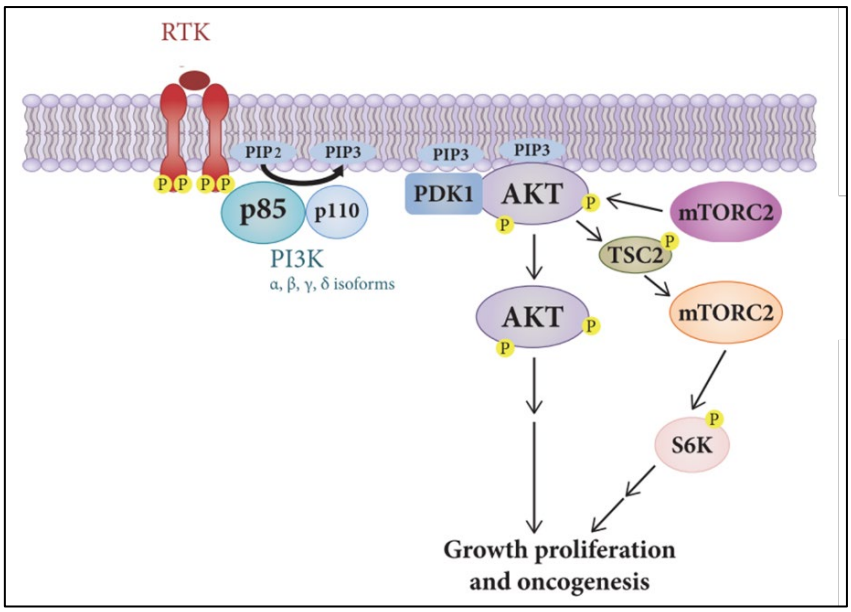

Figure 1 Activation of the phosphatidylinositol 3-kinase (PI3K) pathway leads to downstream signalling cascade through the PI3K/AKT/mTOR.

Source: Adapted from Overview of the relevance of PI3K pathway in HR-positive breast cancer (Vasan N et al 2019) an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC).

Abbreviations: AKT=serine/threonine kinase; mTORC2=mammalian target of rapamycin complex 2; P=phosphorus; p85=regulatory subunit of PI3K; p110=catalytic subunit of PI3K; PDK1=phosphoinositide-dependent kinase 1; PI3K= phosphoinositide 3-kinase; PIP2=phosphatidyl-inositol-diphosphate; PIP3=phosphatidylinositol-triphosphate; RTK=receptor tyrosine kinases; S6K=ribosomal s6 protein kinase; TSC2= tuberous sclerosis complex 2

In BC, dysregulation in the PI3K/AKT/mTOR pathway occurs due to genetic variants in *PIK3CA* (catalytic subunit of PI3K) and/or *AKT*, RTK overexpression and/or loss of function of PTEN tumour suppressor (Vasan et al. 2019). PTEN abrogates PI3K activation by converting PIP3 back to PIP2, and decreased *PTEN* expression leads to activation of the PI3K/AKT/mTOR pathway and increased downstream signalling cellular activities (Reinhardt et al. 2022).

PIK3CA *variants*

The *PIK3CA* gene encodes for the p110α catalytic subunit, and its genetic variation results in constitutive enzymatic activity and unregulated activation of the PI3K pathway (Vasan et al. 2019). *PIK3CA* variation is the most common cause of PI3K pathway variations in BC and affects up to 40% of patients with HR+/HER2- BC (Schagerholm et al. 2024; Vasan et al. 2019). In Australia, *PIK3CA* variants are found in 30% of patients with BC and the concordance between primary and metastatic samples is 69% (n=20/29 patients) (van Geelen et al. 2020). Patients who have BC with a *PIK3CA* variant can exhibit a single hotspot variant, a single non-hotspot variant or multiple variants. The most common single hotspot variant was at H1047 (35-41%), followed by E545 (19-23%) and E542 (7-13%) (Chen et al. 2022).

Patients with *PIK3CA* variants and HR+/HER2- mBC appeared to be resistant to chemotherapy and had worse overall survival, compared to patients with wild-type *PIK3CA* (Mosele et al. 2020). Furthermore, patients with *PIK3CA* variants, HR+/HER2- early-stage BC, and treated with aromatase inhibitor (AI) as adjuvant therapy, were associated with worse prognostic impacts, when compared to patients with wild-type *PIK3CA* (Reinhardt et al. 2022). This suggests *PIK3CA* variation is associated with resistance to AI therapy (Reinhardt et al. 2022).

Treatment options

In Australia, the 1L treatment for HR+/HER2- mBC is ET with or without a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor (BCNA 2020). ET includes tamoxifen, fulvestrant, toremifene and AI (such as anastrozole, letrozole, exemestane). CDK4/6 inhibitors include palbociclib, ribociclib and abemaciclib (BCNA 2020). Ribociclib/abemaciclib + AI/fulvestrant are TGA-approved and PBS-listed as initial therapy or subsequent therapy following prior ET for HR+/HER2- LA/mBC (DHAC 2021; DHAC 2022). Fulvestrant + palbociclib is also TGA-approved and PBS-listed as an initial therapy or continuing therapy, noting that it may only be used as an initial therapy for patients who have recurrence or progressive disease despite prior ET for advanced or metastatic disease with fulvestrant only (DHAC 2022). Table 2 summarises the 1L treatment options based on the ESMO guidelines (2021) and NCCN Breast Cancer guidelines (2024).

Table 2 First line treatment options for patients with HR+/HER2- locally advanced or metastatic breast cancer.

Setting/Guidelines	First line treatment options
Australian clinical practice	ET[a] +/- CDK4/6 inhibitor[b]
ESMO guidelines (2021)	Preferred: • AI[c] + CDK4/6 inhibitor • Fulvestrant + CDK4/6 inhibitor
	Others: • ET monotherapy
NCCN Breast Cancer guidelines (2024)	Preferred: • AI + CDK4/6 inhibitor • Fulvestrant + CDK4/6 inhibitor
	Others: • Fulvestrant + AI • Fulvestrant monotherapy • AI monotherapy • SERM monotherapy

Abbreviations: AI=aromatase inhibitor; ET=endocrine therapy; ESMO = European Society for Medical Oncology; CDK=cyclin D-dependent kinase; HR+/HER2-= hormone receptor positive, human epidermal growth factor receptor 2 negative; NCCN = National Comprehensive Cancer Network; SERM=selective estrogen receptor modulator.

Note: Grey shading indicates applicant's proposed comparator, as aligned with key trial INAVO120.

[a] Endocrine therapy includes aromatase inhibitor, fulvestrant and tamoxifen (SERM).
[b] CDK4/6 inhibitor includes palbociclib, ribociclib and abemaciclib.
[c] Aromatase inhibitor includes anastrozole, letrozole and exemestane.

Targeted treatment for patients with *PIK3CA* variants is recommended as second line (2L) and subsequent line therapy for HR+/HER2- mBC in most guidelines. The National Institute for Health and Care Excellence (NICE 2022), ESMO guidelines (2021) and NCCN Breast Cancer guidelines (2024) recommended alpelisib + fulvestrant as a 2L treatment option in patients with HR+/HER2- LA/mBC with *PIK3CA* variants, after disease progression with AI + CDK4/6 inhibitor. Alpelisib is the first PI3K inhibitor licensed with the United Kingdom's Medicines and Healthcare Products Regulatory Agency, and it has high selectivity for the catalytic subunit alpha of PI3K, for targeted treatment of HR+/HER2- LA/mBC with *PIK3CA* variants (NICE 2022). The recommendation of alpelisib was based on SOLAR-1, a phase three randomised controlled trial, where patients with *PIK3CA* variants and treated with alpelisib and fulvestrant showed improvement in PFS with a HR of 0.65 (95% CI: 0.50-0.85) when compared to placebo and fulvestrant (Gennari et al. 2021). Furthermore, alpelisib + fulvestrant was advised as a 2L therapy as a result of favourable efficacy/toxicity demonstrated by ET + CDK4/6 inhibitor as 1L therapy (Gennari et al. 2021).

Alpelisib + fulvestrant was TGA-approved and indicated for the treatment of postmenopausal women and men with HR+/HER2- advanced or mBC with a *PIK3CA* mutation as detected by a validated test following progression on or after an endocrine-based regimen (DHAC 2024). However, neither alpelisib nor any other *PIK3CA* inhibitor is currently PBS-listed in Australia. NCCN Breast Cancer guidelines (2024) recommended capivasertib + fulvestrant as 2L and subsequent line therapy in patients with HR+/HER2- mBC with *PIK3CA, AKT1* or *PTEN* variants. The recommendation was based on the CAPItello-291 trial, where the addition of capivasertib to fulvestrant treatment significantly improved PFS with a HR of 0.50 (95% CI: 0.38-0.65) among patients with AKT-pathway altered tumours and HR+/HER2- advanced BC, who

had disease progression during or after previous AI therapy, with or without a CDK4/6 inhibitor, when compared to treatment with fulvestrant alone (Turner et al. 2023).

Capivasertib was registered on the ARTG on 9th May 2024 with the following indication: 'Capivasertib is indicated in combination with fulvestrant for the treatment of adult patients with HR+, HER2- (defined as IHC 0 or 1+, or IHC 2+/ISH-) LA/mBC following recurrence or progression on or after an endocrine based regimen' (DHAC 2024). Neither capivasertib nor any other AKT-pathway inhibitor is currently PBS-listed in Australia.

Referring to the INAVO120 study design, patients with HR+/HER2- LA/mBC with *PIK3CA* variants received either inavolisib, in addition to palbociclib and fulvestrant, or palbociclib and fulvestrant alone (Jhaveri et al. 2023). Treatment with palbociclib and fulvestrant was reasonable and aligned with Australian local clinical practice, ESMO guidelines (2021), and NCCN Breast Cancer guidelines (2024).

Estimates for the size of testing population

The applicant presented the estimated utilisation by the proposed population, as summarised in Table 3 below.

Table 3 Estimated utilisation by the proposed population in 2024

Population	Parameter	Estimates	Sources
A	Incidence of BC in 2024	20,771	(AIHW 2023)
B	Patients who relapsed after surgery or adjuvant therapy	25%	(González-Hurtado et al. 2023)
C	Patients in population B with HR+/HER2- subtype	78%	(Bujak et al. 2020)
D	Patients in population C who will have primary or secondary endocrine resistance	30%	(Hartkopf et al. 2020)
E	Estimate uptake in year 1-3	100%	Applicant's estimate
F	Number of patients who will utilise the proposed technology in year 1 (2024) F = A*B*C*D*E	1,215	p8 of MSAC application 1783

Source: p8 of MSAC application 1783

Abbreviations: AIHW=Australian Institute of Health and Welfare; BC=breast cancer; HR+/HER2-=hormone receptor positive, human epidermal growth factor receptor 2 negative; MSAC=Medical Services Advisory Committee.

The population estimates provided in the application were considered uncertain because estimates of patients who relapsed after surgery or adjuvant therapy (population B) and estimates of patients who will have primary or secondary endocrine resistance (population D), were not verifiable against the sources provided. It was also uncertain whether estimates for population B refer to patients with LA/mBC.

The applicant advised that full assessment of the financial considerations, including the estimates on the proportion of metastatic and endocrine resistant patients, will be provided in the reimbursement submission lodged for MSAC and PBAC consideration.

PASC noted that it is estimated that approximately 1,200 patients per year would utilise the proposed PIK3CA *testing (refer to Table 3 for more detail, and to the 'Estimates for the size of testing population' section of this PICO alluding to the uncertainty in these estimates). In addition, a different estimate of approximately 1,700 patients was also presented in the application; in summary the utilisation estimates*

remain uncertain. Despite the uncertainty in the utilisation estimates, PASC considered that the incremental population growth (and therefore associated cost increase) over time is likely to be small. The cost to the MBS was estimated to be approximately $600,000-$700,000 per year if the cost of the MBS item was $400, although PASC considered that this cost was uncertain and expected that testing using ctDNA would likely have a higher cost. PASC also noted that the population estimates were applicable only if the PIK3CA *test was conducted in patients with HR+/HER2- BC following treatment failure. PASC noted that this population was different from the applicant's proposed test population, which does not include the restriction to patients who have experienced treatment failure. PASC noted that the utilisation estimates may not be applicable if the* PIK3CA *testing were to be conducted in the broader population proposed by the applicant. PASC advised that it was best to target the test to the most appropriate patients who could benefit from the testing (i.e. patients with HR+/HER2- LA/mBC who have relapsed during or after adjuvant endocrine therapy) due to the cost implication with a broader test population.*

Prior tests

- Biopsy and imaging (mammogram, ultrasound, or magnetic resonance imaging) to confirm diagnosis of BC.
- 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 HR status and immunohistochemical evaluation to determine HER2 status.

Intervention

The proposed intervention is a codependent health technology to identify whether a patient is suitable for a particular pharmacological treatment. The proposed investigative technology is somatic genetic testing which uses NGS to detect *PIK3CA* variants in ctDNA (derived from blood sample) or tumour tissue from patients with HR+/HER2- LA/mBC. The use of a trademarked assay for the NGS testing to characterise the *PIK3CA* variants was not specified. Detection of *PIK3CA* variants would inform treatment with inavolisib (a PIK3CA inhibitor). Based on the INAVO120 trial primary analysis, patients tested with one or more *PIK3CA* variants and treated with inavolisib + palbociclib + fulvestrant experienced significant improvement in PFS and OS, compared to treatment with placebo+ palbociclib + fulvestrant.

PASC agreed on the test intervention being PIK3CA *testing (method agnostic) and treatment intervention with inavolisib in eligible patients who have tested positive for* PIK3CA *variants.*

The applicant advised that biopsy of tumour tissue sample for the purpose of pathological assessment is part of routine clinical practice. A re-biopsy may be performed to obtain adequate tumour tissue sample for *PIK3CA* testing in the event of insufficient quality of the original biopsy sample or when the original biopsy is exhausted from prior pathological assessments. For *PIK3CA* testing using ctDNA, collection of a plasma sample is required. The applicant proposed in their application that general practitioners or medical oncologists would provide referrals for pathological assessments to inform decisions on treatment selection in patients with LA/mBC. However, in their draft item descriptor the applicant suggested 'specialist and consultant physicians' as the most appropriate referrers. In the event that a laboratory does not have the equipment required to perform NGS analysis, the pathologist may refer *PIK3CA* testing to a speciality molecular pathology laboratory. *PIK3CA* testing is to be performed in a pathology laboratory by a

molecular pathologist, or laboratory staff working under the direct supervision of the pathologist. All personnel performing molecular pathology testing must be suitably qualified and testing laboratories must hold the appropriate accreditations to offer pathology testing in Australia. These training and accreditation requirements apply to all cancer biomarker tests and are not specific to *PIK3CA* testing.

The applicant suggested that the identification of *PIK3CA* variants using a NGS assay is similar to that of other genes such as the *epidermal growth factor receptor* variants. The key steps undertaken in the assessment of variants using a NGS assay include:

- Isolation of DNA and/or ribonucleic acid (RNA) from a blood plasma sample (ctDNA analysis) or a formalin-fixed, paraffin-embedded tumour sample (tissue analysis)
- Preparation of sequencing libraries
- Enrichment of sequencing libraries for *PIK3CA*
- Analysis and reporting of test results to the referring clinician.

There is growing evidence on the use of ctDNA in the assessment of *PIK3CA* variants in BC. The overall ctDNA sensitivity and specificity were 0.73 (95% CI: 0.70-0.77) and 0.87 (95% CI: 0.85-0.89) respectively, with reference to tissue biopsy, based on an individual patient data meta-analysis (Galvano et al. 2022). Subgroup analysis showed greater sensitivity and specificity with NGS, as compared with the polymerase chain reaction-based (PCR) method. The pooled results were comparable between early and advanced tumour burden, as well as between hotspot variants of E542X/E545X versus H1047X.

PIK3CA *testing based on INAVO120 trial*

In the INAVO120 trial, all patients were assessed as having *PIK3CA* variants by testing of either ctDNA or tumour tissue sample. Of note, 92.6% of the patients in the INAVO120 trial were enrolled using ctDNA testing and 7.4% were enrolled per local tissue testing. The INAVO120 trial was a multinational study including Australia and China. Most of the ctDNA testing was conducted centrally (REDACTED%) using FoundationOne® Liquid CDx (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu).

Based on written communication provided during the pre-PASC stage, the applicant emphasised that there were no protocol-driven criteria to determine whether patients received the ctDNA or tumour tissue in the INAVO120 trial. Patients were eligible to have *PIK3CA* testing performed locally (using ctDNA or tissue) or centrally (ctDNA), regardless of patient clinical features. In addition, local testing using ctDNA or tumour tissue could be conducted with either PCR or NGS, and it is unclear what proportion of samples were tested using PCR in this setting. Of note, a copy of the INAVO120 trial protocol was not available during PICO development. The applicant notified that per-protocol *PIK3CA* testing of blood samples or tumour tissue (fresh or archival tumour tissue, with preference for metastasized tissue in local testing) was conducted during screening period, which was between 1 and 28 days prior to the initiation of treatment in the INAVO120 trial.

In correspondence with the Department, the applicant advised that an applicant-convened clinical advisory board, held on 24th June 2024, suggested that *PIK3CA* testing using tumour tissue would likely be requested if tumour tissue (fresh or archival) was available. In the event tumour tissue is not available, ctDNA testing would appear to be more feasible. Moreover, the applicant stated that the advisory board

clinicians did not strongly propose for follow-up tumour tissue testing if ctDNA testing was negative (this contradicts with the recommendations from international guidelines – see below). The applicant clarified that the low number of patients in the tumour testing subgroup in the INAVO120 trial was considered to limit the ability to reliably assess for potential differences in efficacy between the ctDNA and tumour testing subgroups.

Based on the applicant's response to the Department's enquiry at the pre-PASC stage, the applicant provided the eligible *PIK3CA* variants as defined in the INAVO120 trial protocol: H1047D/I/L/N/P/Q/R/T/Y; G1049A/C/D/R/S; E545A/D/G/K/L/Q/R/V; E453A/D/G/K/Q/V; E542A/D/G/K/Q/R/V; K111N/R/E; Q546E/H/K/L/P/R; G106A/D/R/S/V; N345D/H/I/K/S/T/Y; G118D; C420R; R88Q; M1043I/T/V.

PASC noted that PIK3CA *testing using ctDNA was the test used for the majority of participants in INAVO120, while a small proportion used tumour tissue testing. Given that tumour testing is widely used in Australia compared to ctDNA testing, PASC queried the reasoning for performing ctDNA testing over tumour tissue testing. The applicant suggested that testing using ctDNA may be preferred over tumour tissue in instances where tumour tissue is not accessible (for example in the case of bone metastases). In these cases, ctDNA testing via a blood test offers convenience in terms of being able to obtain the most recent sample or a metastatic sample.*

ctDNA testing using FoundationOne® Liquid CDx

FoundationOne® Liquid CDx is an FDA-approved in vitro diagnostic (IVD) companion device which targets 324 genes from ctDNA isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients (Foundation Medicine 2021; Woodhouse et al. 2020). The assay is able to detect substitutions, indels, genomic rearrangements, copy number alterations, and genomic signatures including blood tumour mutational burden, microsatellite instability and tumour fraction (Woodhouse et al. 2020). According to the manufacturer specifications, FoundationOne® Liquid CDx provides complete exonic (coding) coverage of *PIK3CA*, meaning that this test will be able to identify all variants defined in the key trial (as provided by the applicant). The clinical validation for detection of *PIK3CA* variants in ctDNA using FoundationOne® Liquid CDx, versus tumour tissue-based PCR clinical trial assay (as utilised in the SOLAR-1 trial), and ctDNA using FoundationOne® Liquid CDx against cell-free-based (liquid biopsy) NGS, was largely concordant (Woodhouse et al. 2020).

FoundationOne® Liquid CDx Specimen Collection Kit (ARTG ID 425682) was ARTG-listed on 16th October 2023, and it is intended to allow the collection and transport of whole blood, from the specimen collection site to the clinical laboratory, for the purpose of testing with the FoundationOne® Liquid CDx Assay. However, FoundationOne® Liquid CDx assay is currently not registered on the ARTG as a 'companion diagnostic'.

PIK3CA *testing based on international guidelines*

The ESMO guidelines (2021) for the management of mBC recommend that *PIK3CA* should be tested, whether using tumour tissue or ctDNA, as part of routine clinical practice, only if the results of the assessment will change the treatment approach (Gennari et al. 2021). The NCCN Breast Cancer guidelines (2024) recommend testing for *PIK3CA* variants using tumour tissue or ctDNA from peripheral blood, to identify candidates for alpelisib plus fulvestrant, in patients with HR+/HER2- mBC. If testing using ctDNA is negative, tumour tissue testing is recommended (NCCN Breast Cancer 2024, Henry et al. 2022). This

recommendation was based on the low agreement between plasma ctDNA and tumour tissue identification of *PIK3CA* variants via PCR in SOLAR-1 trial (Henry et al. 2022). Among patients with confirmed *PIK3CA* variants using tumour tissue, only 56% showed positive *PIK3CA* variants using ctDNA (Henry et al. 2022). Furthermore, the American Society of Clinical Oncology 2022 (ASCO) guidelines suggested to test the most recent metastatic tumour tissue sample as *PIK3CA* variants may be acquired during treatment and therefore it is possible for *PIK3CA* variants status to change from the original primary breast tumour (Henry et al. 2022). ctDNA may be the preferred first step if no recent tumour tissue sample is available (Henry et al. 2022).The guideline also recommended testing of a tumour specimen (preferably from a metastatic site) in the event the ctDNA result was negative.

Challenges with PIK3CA *testing using tumour tissue and ctDNA*

There are various biopsy and analytical testing approaches to detect *PIK3CA* variants but the generalisability and applicability across approaches is uncertain: the concordance data between testing methods; site of sample collection (e.g. primary tumour vs metastasis); timing of sample collection (e.g. fresh biopsy vs archival tissue); type of biopsy (e.g. ctDNA vs tissue); retest concordance (i.e. stability over time) were lacking (Anderson et al. 2020).

PASC asked the applicant whether there is the potential for PIK3CA *status to change over time and if this would influence whether ctDNA or tumour tissue testing would be the preferred test, given that ctDNA testing can be performed less invasively and more quickly than tumour tissue testing. The applicant suggested that there is the potential for DNA alteration to occur in the time between the diagnosis of primary and metastatic tumours, but some studies suggest that the majority of* PIK3CA *mutations are detected in the primary tumour. The applicant noted there are some medical oncologists who believe that DNA alterations are likely present from the beginning of the disease process. PASC noted that the understanding around changing* PIK3CA *status is still an evolving field.*

The applicant referred to the ongoing engagement with its global clinical team to work towards providing concordance data regarding PIK3CA *testing for tumour tissue vs ctDNA from the screening phase of INAVO120. This will include a subgroup analysis of the INAVO120 trial analysing the outcomes for patients enrolled based on* PIK3CA *testing performed using tumour tissue vs ctDNA. The applicant stated that the data will be included in the assessment report, depending on availability.*

Further uncertainties in the use of ctDNA include variable detection rate of *PIK3CA* variants between shorter and longer DNA fragments of ctDNA (Vollbrecht et al. 2023). Shorter DNA fragments were observed in the bloodstream as a result of DNA shedding from cancer cells (Chen et al. 2023). Vollbrecht et al. found that longer fragments of ctDNA led to higher specificity and sensitivity for *PIK3CA* variants detection. They suggested that assays specifically designed for *PIK3CA* variants detection in ctDNA should be used to prevent false-negative results (Vollbrecht et al. 2023). In addition, the FoundationOne® Liquid CDx technical information recommended blood collection for ctDNA testing to be conducted prior to therapy or at a time of disease progression, in order to obtain optimal ctDNA shed (Foundation Medicine 2023). This is because the assay performance is correlated to the level of ctDNA shed (Foundation Medicine 2023). Furthermore, a low ctDNA tumour fraction may result in false negative results and may inform the need for follow-up tissue testing, in case of negative ctDNA testing (Rolfo et al. 2024).

PASC acknowledged that ctDNA is released in small quantities into the bloodstream and therefore sensitive detection methods are needed. The applicant also noted that sensitivity is an issue for ctDNA testing, where in some instances variants may not be detected. A low ctDNA tumour fraction (<1%) in the bloodstream

may result in a false negative result. Hence, technical adaptions (deep sequence coverage, molecular barcoding and error correction algorithms) are needed for NGS-based ctDNA testing.

PIK3CA *testing in Australia*

The applicant had conducted a review of somatic *PIK3CA* testing currently offered by Australian laboratories, as published by The Royal College of Pathologists of Australasia (RCPA). According to this review, *PIK3CA* testing using NGS is currently being offered by several Australian pathology laboratories within the scope of their National Association of Testing Authorities (NATA) accreditation. The department noted that *PIK3CA* testing for certain variants is also offered through Peter MacCallum Cancer Centre using digital droplet PCR (for ctDNA samples).

Of note, *PIK3CA* tests were commonly offered as part of panel testing by Australian laboratories, and the coverage of *PIK3CA* hotspots varied based on the assays used. It is unclear whether all relevant *PIK3CA* variants can be detected by each of these assays. In addition, laboratories in Australia use various in-house NGS assays and IVDs, in which further concordance assessment is necessary. Furthermore, the availability and accessibility of *PIK3CA* testing using ctDNA in Australia is uncertain.

PASC advised that PIK3CA *is a very common oncogene found in many different cancers, and therefore can be readily tested for using tumour tissue and can be found on many existing NGS gene panels. Since* PIK3CA *is likely included in many existing gene panels, PASC noted that PIK3CA may already be sequenced in many cases, without being analysed or reported on.*

*PASC also considered that many clinicians may prefer multigene panel testing, rather than single gene testing, because it allows for selection of different treatment regimens based on a single report, rather than retesting for a particular gene. PASC noted MSAC Application 1766, which requested MBS listing of tumour tissue testing to characterise genetic variants in the AKT pathway (*PIK3CA, AKT1 *and* PTEN *genes) also include* PIK3CA *testing, but has not yet been considered by MSAC.*

PASC had concerns regarding the implementation of PIK3CA *testing using ctDNA in Australia. PASC noted that limited laboratories currently offer ctDNA testing in Australia. PASC noted that the Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP) are partnered with the European Molecular Genetics Quality Network (EMQN) for the provision of their External Quality Assessments (EQA), and that many Australian diagnostic laboratories participate in EMQN EQA schemes. PASC noted that the EMQN has run a pilot EQA scheme for breast cancer* ESR1 *testing in plasma. To date, no EQA schemes appear to have been run for PIK3CA testing using ctDNA in Australia.*

Based on a written communication provided at the pre-PASC stage, the applicant noted that they were not aware of any concordance studies between FoundationOne® Liquid CDx and specific test(s) that are performed locally. In response, the Department advised that the proposed test intervention needs to be an appropriate test, with a high level of concordance with the clinical utility standard, and has completed the regulatory requirements to be eligible for public funding under the MBS. Furthermore, the MSAC-PBAC codependent process is intended to ensure patients have funded access to both the MBS service and medicine.

PIK3CA testing could be performed using an ARTG-approved IVD such as Therascreen® PIK3CA RGQ PCR kit (ARTG ID 330843). Of note, Therascreen® PIK3CA RGQ PCR kit is intended for use as a companion diagnostic test, to aid clinicians in the identification of breast cancer patients who may be eligible for treatment with alpelisib based on a *PIK3CA* mutation detected result. The Therascreen® PIK3CA RGQ PCR

Kit could detect 11 *PIK3CA* variants using DNA extracted from tumour tissue or ctDNA in plasma (DoH TGA 2020).

PASC's advice was sought on:

1. Given that *PIK3CA* testing using digital droplet PCR is currently available in Australia (using ctDNA samples), should this test also be considered in the assessment phase of this application? Note that the currently available assay only tests for certain variants and not for all *PIK3CA* variants defined in the key trial protocol.
2. Could testing with Therascreen® PIK3CA RGQ PCR Kit using tumour tissue or ctDNA inform treatment eligibility to other *PIK3CA* inhibitors such as inavolisib?

PASC noted that there are non-NGS methods such as digital droplet PCR and a PIK3CA *PCR kit in Australia, but that these methods may not detect all* PIK3CA *variants listed in the INAVO120 trial, in which there were approximately 60 variants that were eligible for enrolment into the trial. PASC noted from the applicant comment that FoundationOne® Liquid CDx (for ctDNA) and FoundationOne® CDx (for tumour tissue) NGS methods used in the trial were able to identify all known* PIK3CA *variants. PASC considered that if real-world testing does not reflect this (i.e. if other tests used in practice do not detect the full range of variants detected in INAVO120), the real-world cost-effectiveness of treatment will be lower than expected if trial data is used to produce the economic model. PASC queried the number of* PIK3CA *variants found in patients in the INAVO120 trial, noting that INAVO120 was a small trial and there may be other possible variants in patients beyond those identified in the trial. The applicant noted that a small subset of the eligible variants (~4-5 variants) represented most of the enrolled patients (~80%). Given that only a small subset of* PIK3CA *variants were identified in the majority of the trial population, PASC considered that it is reasonable for non-NGS methods (which may not pick up all of the ~60 eligible PIK3CA variants) to be used in clinical practice. Furthermore, PASC noted that these alternative testing methods could be used since MBS items are preferably method agnostic, allowing individual laboratories to decide on their preferred method of testing (e.g., based on test accuracy). PASC also noted that since preferred testing methods were market-driven, inaccurate methods will likely be phased out, and therefore not restricting testing to a specific method was reasonable. Although the MBS item will likely be method agnostic, PASC considered that in practice majority of laboratories are likely to use the already available and validated NGS panels for tumour tissue testing (which includes* PIK3CA *testing) and therefore considered that the assessment should focus on NGS testing methods.*

Comparator(s)

Test comparator

The proposed test comparator is 'no testing' for *PIK3CA* genetic variation(s). Prior to this application, there was no subsidised test available to determine *PIK3CA* variants status or to guide targeted treatment in HR+/HER2- LA/mBC. There were two relevant PICO confirmations for *PIK3CA* testing (MSAC application 1604 and 1766), and both nominated "no testing" as the test comparators.

Treatment comparator

The proposed treatment comparator is palbociclib + fulvestrant. Palbociclib + fulvestrant are currently PBS-listed for the treatment of HR+/HER2- LA/mBC in patients who had received previous ET. It is reasonable to

include palbociclib + fulvestrant as comparators based on the key trial INAVO120, and it aligns with the current standard practice in Australia, which is ET with or without CDK4/6 inhibitor for 1L treatment of HR+/HER2- LA/mBC. Although there are other PBS-listed CDK4/6 inhibitors such as abemaciclib and ribociclib, these CDK4/6 inhibitors may be used in patients who have not received prior ET for mBC. On the other hand, palbociclib + fulvestrant is restricted to patients with prior ET, which aligns with the key trial INAVO120. The appropriate treatment comparator is a matter for PBAC consideration.

PASC advised that no PIK3CA *testing was the appropriate test comparator. PASC considered current standard of care was likely to be the appropriate treatment comparator, noting that treatment is a matter for PBAC consideration.*

Reference standard (for investigative technologies only)

There is no reference standard for *PIK3CA* genetic variation(s) testing in Australia. In this case, the accuracy of the proposed test may need to be demonstrated by direct from test to health outcomes evidence showing a health benefit resulting from use of test, or by a comparison against a suitable clinical utility standard.

PASC acknowledged that there was no reference standard for PIK3CA *testing in Australia.*

Clinical utility standard (for codependent investigative technologies only)

A reference standard is not currently available for the proposed *PIK3CA* testing. Therefore, the accuracy of the *PIK3CA* testing needs to be demonstrated by comparison against a suitable clinical utility standard, which is likely to be FoundationOne® Liquid CDx. Communication received from the applicant at the pre-PASC stage stated that the majority of patients in the INAVO120 trial were tested through central testing using FoundationOne® Liquid CDx. Of note, central ctDNA testing was also conducted using PredicineCARE NGS assay (Huidu) in China, of which the data was unavailable during PICO development. Only 7.4% of the patients were enrolled using tumour tissue testing and REDACTED% of the patients were tested using ctDNA local testing.

FoundationOne® Liquid CDx Specimen Collection Kit is registered on the ARTG and is available in Australia. However, FoundationOne® Liquid CDx assay is not registered as a 'companion diagnostic' with the TGA. Also, the PredicineCARE NGS assay utilised in the INAVO120 trial is currently not registered on the ARTG. It is not clear how many participants were tested using the FoundationOne® Liquid CDx assay vs the PredicineCARE NGS assay in the INAVO120 trial and the applicant was asked to provide this information.

The applicant clarified that FoundationOne® Liquid CDx and PredicineCARE NGS assay (Huidu) were not the same test and the majority of the patients enrolled in INAVO120 were tested with FoundationOne® Liquid CDx, which is currently not listed on the ARTG. Specifically, the applicant advised that REDACTED% of the cohort enrolled in INAVO120 were based on central testing using ctDNA, of which REDACTED% were from outside China and were tested using the FoundationOne® Liquid CDx assay, and only REDACTED% were from China and were tested using the PredicineCARE NGS assay. PASC advised that FoundationOne® Liquid CDx was a reasonable clinical utility standard as it was the most used method in the INAVO120 trial.

Outcomes

The following test and treatment outcomes are applicable for this co-dependent MSAC/PBAC application:

Test outcomes

Efficacy/effectiveness

- Analytical performance, diagnostic and predictive accuracy of the proposed *PIK3CA* variants testing using NGS (sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)).
- Comparison of the analytical performance (concordance and discordance) of the proposed *PIK3CA* variants testing using NGS (for both ctDNA and tumour tissue) to the clinical utility standard (no reference standard).
- Comparison of *PIK3CA* variants tests using NGS (commercial and in-house developed) that are likely to be used in Australia, considering both ctDNA and tumour tissue tests.
- Comparative diagnostic accuracy between ctDNA from blood sample and tumour tissue sample (fresh/archival/primary/metastasis sample) in the identification of *PIK3CA* variants.
- Clinical validity of test:
    - Differential prognostic effect of the proposed *PIK3CA* variants testing in LA/mBC, particularly including an assessment of whether this prognostic effect varies further according to whether the patient is positive or negative for *PIK3CA* variants.
- Clinical utility of test:
    - Treatment effect modification of inavolisib as a consequence of *PIK3CA* status from testing using ctDNA or tissue sample.
    - Whether *PIK3CA* variants testing provides predictive value in determining which patients are likely to respond most to inavolisib.
- Other test related considerations:
    - Test turnaround time.
    - Test failure rates and re-biopsy rates (if tumour tissue sample).

Safety outcomes

- Adverse events associated with collection of plasma sample for ctDNA analysis, biopsy for tumour tissue testing, and re-biopsy (e.g. for patients with an inadequate tissue sample for tumour testing).

Healthcare resources

- Estimated number of patients to be tested.
- Cost of test intervention and associated delivery cost.
- Cost of re-biopsy (if tumour tissue sample).
- Cost of blood plasma collection.
- Cost of re-test (if tumour tissue testing is conducted after a negative ctDNA test).

Treatment outcomes

Efficacy/effectiveness

- PFS.
- OS.
- Response rate.
- Quality of life.
- Comparative effectiveness of treatment based on tumour and ctDNA variant status.

Safety Outcomes

- Comparative safety and tolerability of inavolisib (in combination with palbociclib + fulvestrant), compared to alternative first line treatments in patients with/without *PIK3CA* variants, assessed by adverse events, discontinuation rates, deaths and collection of clinical chemistry/haematology parameters.

Healthcare resources

- Cost of treatment intervention.

Total Australian Government Healthcare costs

- Total cost to the MBS.
- Total cost to the PBS.
- Total cost to other healthcare services.

PASC confirmed that the outcomes listed in the PICO were appropriate.

Assessment framework (for investigative technologies)

The assessment framework conceptually outlines the steps from the test population to the final health outcomes, as shown in Figure 2.

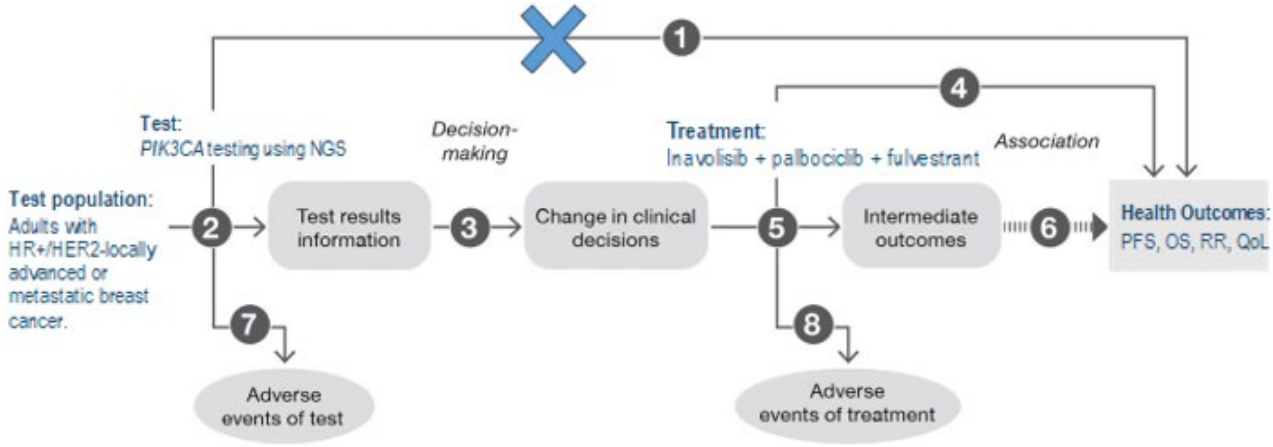

Figure 2 Assessment framework showing the links from the test population to health outcomes

Source: Adapted from Figure 8, p76 of Guidelines for preparing assessments for the Medical Services Advisory Committee version 1.0 May 2021

Abbreviations: ET = endocrine therapy; HR+/HER2-=hormone receptor positive, human epidermal growth factor receptor 2 negative; LA/mBC=locally advanced or metastatic breast cancer; NGS=next generation sequencing; OS=overall survival; *PIK3CA*=phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS=progression free survival; QoL=quality of life; RR=response rate.

Notes: 1: no direct from test to health outcomes evidence; 2: test accuracy; 3: change in management based on test results; 4: influence of the treatment with inavolisib + palbociclib + fulvestrant 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

The target test population is adults with HR+/HER2- LA/mBC, whose disease progressed during treatment or within 12 months of completing adjuvant ET, which is aligned with the INAVO120 trial population, and PASC's advice. The target test population is to be offered genetic testing using NGS, with the purpose of identifying *PIK3CA* variants in ctDNA or tumour tissue. The test outcomes can be positive or negative for *PIK3CA* variants. Patients with a positive test outcome are then eligible for treatment with inavolisib + palbociclib + fulvestrant. In the INAVO120 primary analysis, treatment with inavolisib + palbociclib + fulvestrant in patients who tested positive with one or more *PIK3CA* variants resulted in significant improvement in PFS and OS (interim analysis).

Referring to Figure 2, the key assessment questions related to the assessment framework are:

i. What is the test accuracy (sensitivity, specificity, PPV, NPV) of the proposed *PIK3CA* testing using NGS, against the clinical utility standard (no reference standard)?
ii. As there are *PIK3CA* tests available in Australia but are currently not listed on the MBS (e.g. AKT-pathway testing and TGA-approved companion diagnostic test to detect *PIK3CA* variants which inform treatment with alpelisib), are these tests concordant with the proposed test intervention and/or clinical utility standard?
iii. Does the test outcome, whether positive or negative for *PIK3CA* variants, lead to a change in the management of the test population?

iv. What is the effect of inavolisib + palbociclib + fulvestrant on health outcomes in patients with and without *PIK3CA* variants, or with unknown *PIK3CA* status?
v. What are the adverse events related to the test and treatment intervention?

PASC considered that the assessment framework was appropriately described in the PICO.

Clinical management algorithms

The applicant-proposed clinical management algorithms without and with *PIK3CA* testing and inavolisib are presented in Appendix 1.

Current clinical management algorithm

The applicant-proposed current clinical management algorithm representing the current situation without *PIK3CA* testing and inavolisib (Appendix 1). The algorithm was updated by the assessment group during PICO development, which is illustrated in Figure 3.

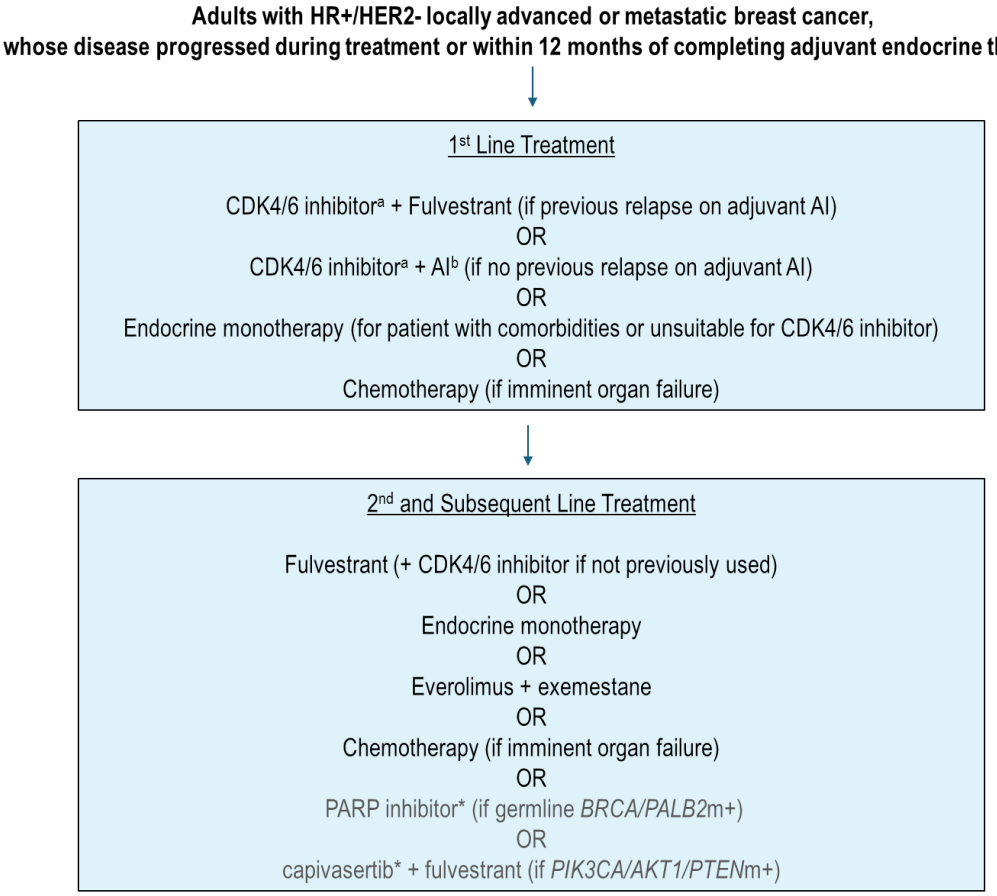

Figure 3 Current clinical management algorithm for adults with HR+/HER2- locally advanced or metastatic breast cancer, who have relapsed during or after endocrine therapy.

Source: adapted from Figure 1, p13 of MSAC application 1783 PICO set

Abbreviations: 1st=first; 2nd=second; AI=aromatase inhibitor; *BRCA*=Breast Cancer gene; CDK4/6 inhibitor=cyclin dependent kinase 4 and 6 inhibitor; HR+/HER2-=hormone receptor positive, human epidermal growth factor receptor 2 negative; *PALB2m+*= Partner and localizer of *BRCA2* positive; PARP=Poly (ADP-ribose) polymerase; *PIK3CA/AKT1/PTENm+*= positive variant of either phosphatidylinositol-4,5-bisphosphate-3-kinase catalytic subunit α/serine-threonine kinase 1/phosphatase and tensin homologue.

[a] CDK4/6 inhibitor listed on the PBS are abemaciclib, palbociclib and ribociclib.

[b] AI listed on the PBS are anastrozole, letrozole and exemestane.

* Grey text indicates non-PBS listed treatment options for this context. Of note, PARP inhibitor olaparib was recommended in the July 2024 PBAC meeting.

In contrast to the applicant's algorithm, Figure 3 considers the test population to be adults with HR+/HER2- LA/mBC, whose disease progressed during treatment or within 12 months of completing adjuvant ET, which is aligned with the INAVO120 trial population, and the test population was confirmed by PASC. Two additional 1L treatment options were added to the algorithm: ET monotherapy (for patients with comorbidities or unsuitable for CDK4/6 inhibitor) and chemotherapy (if imminent organ failure). These two treatment options are available to patients treated in Australia (Cancer Council Victoria and Department of Health Victoria 2021), and are aligned with the ESMO guidelines (2021) (Gennari et al. 2021). Figure 3 also included 2L and subsequent line treatment with a PARP inhibitor or capivasertib + fulvestrant. The PARP inhibitor olaparib was discussed and subsequently recommended in the July 2024 PBAC meeting for HER2-

mBC with confirmed *BRCA1/2* variants, while capivasertib is TGA-approved but not yet PBS-listed. Olaparib and capivasertib are available to self-funded patients in Australia.

Clinical management algorithm with PIK3CA *testing and inavolisib*

The ESMO guidelines (2021) recommended the assessment of *PIK3CA* status in all patients with newly diagnosed or recurrent mBC with HR+/HER2- tumours. *PIK3CA* testing should only be carried out as part of routine clinical practice if the results will change the treatment approach (Gennari et al. 2021). NCCN Breast Cancer guidelines (2024) recommended *PIK3CA* variant testing should be performed using either tumour tissue or ctDNA, and if ctDNA shows negative results, tumour tissue testing is recommended.

PASC's advice was sought regarding the order in which ctDNA and tumour tissue testing should be performed. The applicant has not suggested specific criteria regarding the choice of sample type or sequence of testing. The applicant stated in the pre-PASC teleconference that there were no specific criteria for choice of test in the INVAO120 trial. A revised algorithm was proposed by the assessment group and the department at the pre-PASC stage which specified *PIK3CA* testing should occur via ctDNA first and then be followed by tumour tissue testing if ctDNA test results are negative for one or more *PIK3CA* variants, to align with the ASCO guideline (Henry et al 2022).

The applicant advocated for flexibility on whether to perform tumour testing or ctDNA testing to accommodate different clinical scenarios. PASC advised that the clinical algorithm would likely be dependent on the concordance data between ctDNA and tumour tissue, which is currently pending. If the data shows high concordance, the proposed PIK3CA *test can be performed using either ctDNA or tumour tissue. However, PASC noted the advantages, limitations, uncertainty and feasibility of ctDNA testing. PASC therefore considered that if concordance is not high, then there may be a need to include confirmatory testing within the algorithm following a negative test, due to the possibility of false negative results, although this will be dependent on the concordance data (if available) and its reliability. The applicant agreed and added that most patients in INAVO120 trial were tested with FoundationOne® Liquid CDx (for ctDNA) and FoundationOne® CDx (for tumour tissue), and these two assays were designed with concordance in mind. Therefore, the applicant expected high concordance between these two assays but was uncertain with how this compared with the range of tests available in Australia.*

Figure 4 illustrates the revised clinical management algorithm with *PIK3CA* testing and inavolisib, based on the applicant's proposed algorithm and PASC advice.

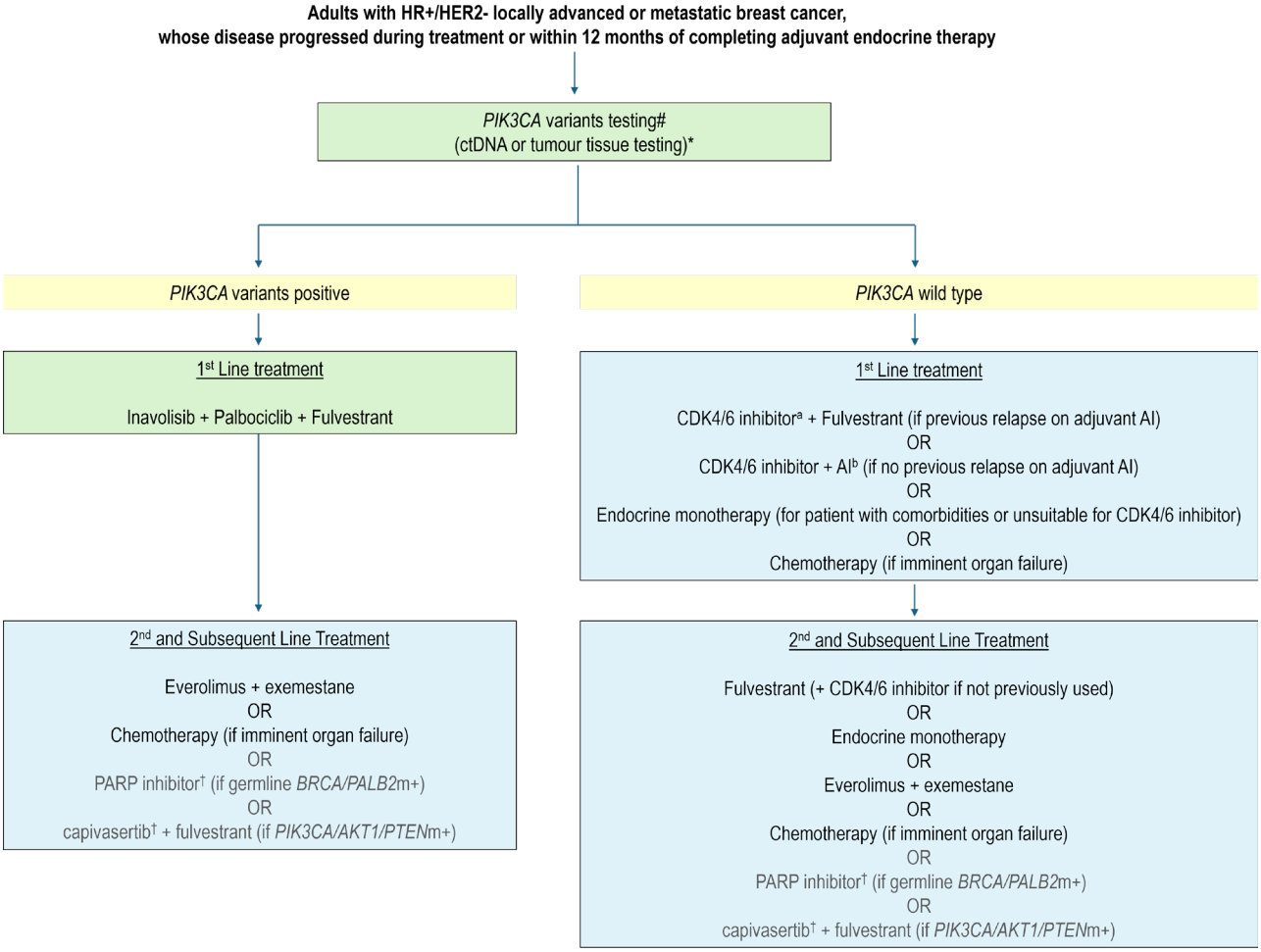

Figure 4 Clinical management algorithm with *PIK3CA* testing and inavolisib, for adults with HR+/HER2- locally advanced or metastatic breast cancer, who have relapsed during or after endocrine therapy.

Source: adapted by the assessment group and the department from Figure 2, p14 of MSAC application 1783 PICO set

Abbreviations: AI=aromatase inhibitor; *AKT*=serine/threonine kinase; *BRCA*=Breast Cancer gene; CDK4/6 inhibitor=cyclin dependent kinase 4 and 6 inhibitor; ctDNA=circulating tumour deoxyribonucleic acid; HR+/HER2-=hormone receptor positive, human epidermal growth factor receptor 2 negative; *PALB2m*+= Partner and localizer of *BRCA2* positive; PARP=Poly (ADP-ribose) polymerase; *PIK3CA/AKT1/PTENm*+= positive variants of either phosphatidylinositol-4,5-bisphosphate-3-kinase catalytic subunit α/serine-threonine kinase 1/phosphatase and tensin homologue.

Notes: Green shaded boxes highlight proposed changes to current algorithm. Yellow shaded boxes indicate outcomes of *PIK3CA* testing. Blue shaded boxes outline the current treatment options in Australia.

[a] CDK4/6 inhibitor listed on the PBS are abemaciclib, palbociclib and ribociclib.

[b] AI listed on the PBS are anastrozole, letrozole and exemestane.

*If concordance data between ctDNA and tumour tissue is not high, a confirmatory test following negative testing may be required. Most recent tumour tissue sample from a metastatic site should be used, when possible, due to the possibility of *PIK3CA* variant status changing during treatment since the diagnosis of the primary breast tumour.

Germline *BRCA*, *PALB2* and AKT pathway testing may also be done at this time, if not already done previously. However, the position of these tests in the clinical pathway is yet to be confirmed, pending MSAC decision on applications 1507.1 (for *BRCA* testing) and 1766 (for AKT pathway testing).

† Grey text indicates non-PBS listed treatment options for this context. Of note, PARP inhibitor olaparib was recommended in the July 2024 PBAC meeting.

In contrast to the applicant's proposed algorithm, Figure 4 includes the following:

- Test population: Adults with HR+/HER2- LA/mBC, whose disease progressed during treatment or within 12 months of completing adjuvant ET, as confirmed by PASC.
- Test intervention: *PIK3CA* variants testing using ctDNA or tumour tissue. Depending on the concordance data between ctDNA and tumour testing that is available, confirmatory testing may be required. As advised by PASC, if ctDNA test results are negative for *PIK3CA* variants, tumour tissue testing, preferably with recent tumour tissue sample from a metastatic site, may be necessary. This testing sequence is aligned with the NCCN Breast Cancer guidelines (2024).
- The algorithm considered germline *BRCA* testing for patients with mBC, alongside 1L treatment with chemotherapy or ET in metastatic setting. However, its position in the algorithm is uncertain. Germline *BRCA* testing is currently not listed on the MBS for this context, and will be discussed in the August 2024 MSAC meeting (MSAC Application 1507.1).
- If patients test positive for *PIK3CA* variants, patients could be eligible for 1L treatment with inavolisib + palbociclib + fulvestrant. Following disease progression, a PARP inhibitor can be considered as an option for 2L and subsequent line treatment in patients with germline *BRCA/PALB2* variants. Of note, PBS-listing of the PARP inhibitor olaparib for this indication was considered and subsequently recommended at the July 2024 PBAC meeting.
- Capivasertib + fulvestrant could be a 2L treatment option, although capivasertib is not currently PBS-listed, for patients with HR+/HER2- mBC and who test positive for *PIK3CA/AKT1/PTEN* (AKT pathway) variants. This scenario was considered by PASC at their April 2024 meeting as part of MSAC application 1766. It is due for further consideration by MSAC in November 2024.
- The placement of AKT-pathway testing in the algorithms is uncertain. As previously mentioned, AKT pathway testing in patients with BC has been previously discussed at PASC in April 2024 (MSAC application 1766).

Alpelisib, a *PIK3CA* inhibitor, is registered with the ARTG for the treatment of men and postmenopausal women with HR+/HER2- advanced or mBC with a *PIK3CA* variant as detected by a validated test following progression on or after an endocrine-based regimen. Based on the ratified PICO of MSAC application 1604, the role of alpelisib as a 1L or 2L treatment option was uncertain, hence it was not included in the algorithm.

The roles of alpelisib or capivasertib or ET as a 2L treatment option in HR+/HER2- mBC with *PIK3CA* variants, after disease progression with inavolisib + palbociclib + fulvestrant, were also uncertain, and these were therefore also not included in the algorithm.

PASC's advice was sought in the event that AKT-pathway testing (MSAC application 1766) is supported by MSAC and subsequently listed on the MBS: Would AKT-pathway testing substitute the proposed *PIK3CA* testing, given AKT-pathway covers all three variants of *PIK3CA, AKT1* and *PTEN*, and considering the importance of *PTEN* status? Of note, PASC suggested that *PTEN* status was an important factor given the loss of inhibition function was related to ET resistance (ratified PICO Application 1766). Specifically, loss of function of *PTEN* can drive resistance to PIK3CA inhibitors and subsequently cause increased downstream cellular signalling (Vasan et al. 2019). Considering AKT-pathway testing uses tumour tissue and the proposed *PIK3CA* testing uses ctDNA or tumour tissue, would a concordance assessment be needed

between these two types of genetic testing, before AKT-pathway testing could be used as a substitute for *PIK3CA* testing?

PASC's advice was sought regarding whether *PIK3CA* testing using ctDNA would be followed by AKT-pathway testing using tumour tissue, if ctDNA testing for *PIK3CA* is negative.

*PASC noted that MSAC Application 1766 has requested testing for AKT pathway alterations (*PIK3CA, AKT1 *and* PTEN*) in BC patients using tumour tissue. It has not been considered by MSAC yet (for further details see above) and therefore PASC deferred any decisions regarding AKT pathway alterations until MSAC's consideration.*

Proposed economic evaluation

The overall clinical claim is for superiority. The applicant claimed that the proposed codependent technology (*PIK3CA* testing and inavolisib + palbociclib + fulvestrant treatment) is superior in terms of comparative effectiveness versus the comparator (no testing and palbociclib + fulvestrant) in patients with HR+/HER2- LA/mBC, who have relapsed during or after ET. The comparative safety of inavolisib to placebo appeared likely inferior, based on the INAVO120 primary analysis. There were more incidents of grade 3 or higher adverse events in the inavolisib group at 92%, vs 83.3% in the placebo group. Grade 3-4 adverse events such as neutropenia, thrombocytopenia, anaemia, stomatitis, hyperglycaemia, diarrhoea and nausea were more commonly reported in the inavolisib group. According to the guidelines for preparing assessments for the MSAC (version 1.2 2021), a cost-utility analysis would be appropriate for this context, as indicated by the grey shaded box in Table 4.

Table 4 Classification of comparative effectiveness and safety of inavolisib, 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

Source: Table 2, p9 of PICO Confirmation Template

Abbreviations: 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

Grey shaded box indicates the suitable economic evaluation for this context.

PASC noted that the proposed economic evaluation was a cost utility analysis, and considered that this was appropriate based on the applicant's claim of superior effectiveness and likely inferior safety.

Proposal for public funding

Currently there is no MBS funded *PIK3CA* testing for either tumour tissue or ctDNA specimen types. The applicant proposed public funding through the MBS, and provided two options for the MBS item descriptor:

- Scenario 1, an amendment of the proposed item descriptor based on the PICO Set Document for MSAC Application 1766, and
- Scenario 2, based on MBS item 73433 as a high-level template.

Of note, the proposed MBS item descriptor from the PICO Set Document for MSAC Application 1766 was updated based on PASC advice and published in the ratified PICO of Application 1766 (April 2024). Further modification of this proposed MBS item descriptor to include ctDNA may not be feasible as the use of ctDNA to characterise *PIK3CA, AKT1* and *PTEN* variants is uncertain. Furthermore, this proposed MBS item descriptor was restricted to patients following recurrence or progression on or after AI therapy, which differed from the current application's population and INAVO120 trial population.

Therefore, the following MBS item descriptor was updated by the assessment group based on the applicant's proposed Scenario 2.

Category 6 – PATHOLOGY SERVICES
MBS item *XXXX ~~Next generation sequencing (NGS) test for~~ A test of tumour tissue or circulating tumour DNA to characterise phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (*PIK3CA*) variants, ~~mutations performed on tumour tissue or circulating tumour DNA (ctDNA) from~~ in a patient with: • locally advanced (inoperable) or metastatic hormone receptor-positive, HER2- breast cancer~~, if:~~ AND • following recurrence or progression on or after adjuvant endocrine therapy. ~~The breast cancer is documented as hormone receptor-positive; and~~ ~~The breast cancer is documented as HER2-negative; and~~ ~~The test is~~ As requested by a specialist or consultant physician, to determine eligibility for a treatment listed on ~~if requirements relating to PIK3CA mutation status for access to a PIK3CA inhibitor under~~ the Pharmaceutical Benefits Scheme for this context. ~~are fulfilled~~ ~~Proposed Applicable only once per lifetime~~ Once per primary tumour diagnosis.
Fee: $350-400 Benefit: 75% = $262.50-300.00 85% = $297.50-340.00

Source: Adapted from Scenario 2, p10 of the submission 1783 PICO Set *PIK3CA* Testing Inavolisib

Yellow highlight indicates text added by the assessment group.

Strikethrough text indicates text deletions suggested by the assessment group.

The proposed MBS item descriptor is silent on test methodology based on the advice of the Department to account for laboratory preferences as well as technological advancements to futureproof the descriptor, as described in the ratified PICO of MSAC Application 1766.

PASC considered it appropriate for the MBS item descriptor to be agnostic as to the testing methodology and drug, and for the item to be "as requested by a specialist or consultant physician".

PASC considered that the item descriptor remaining method agnostic should not result in substandard assays with poor analytical performance. PASC advised that, while not all testing methods are able to detect all relevant PIK3CA *variants (noting that many* PIK3CA *variants exist, many of which are pathogenic), laboratories are likely to adopt the most accurate testing method. PASC therefore considered it likely that NGS would be the preferred method, given its high analytical performance and ability to detect most gene variants and hotspots.*

Further amendment includes "AND following recurrence or progression on or after adjuvant endocrine therapy", to be consistent with the study population in the INAVO120 trial. PASC's advice was sought to confirm the test population in the MBS descriptor.

PASC noted the applicant's proposed change to the MBS item descriptor which involved removing "following recurrence or progression on or after adjuvant endocrine therapy". PASC considered that the applicant's suggestion to remove the disease progression criterion may represent leakage of the test population and may incur significant cost implications.

The proposed MBS item descriptor informs treatment eligibility for a treatment listed on the PBS for the context, and is not restricted to a specific molecule or class of medicines. For example, detection of *PIK3CA* variants in HR+/HER2- mBC could inform treatment with inavolisib or alpelisib or capivasertib, if PBS-listed.

The MBS item was edited to once per primary tumour diagnosis, to allow treatment decision-making for a potential subsequent BC tumour.

PASC also noted the applicant's concern that limiting testing to once per primary tumour diagnosis may preclude additional necessary tests (e.g. confirmatory/follow up testing with a different sample type after a negative test result, if needed). While PASC noted that the original application included a restriction to testing once per lifetime, it agreed that the intent was not to prevent necessary secondary testing. PASC clarified that the restriction to "once per primary tumour diagnosis" in the MBS item descriptor was reasonable, and advised that an explanatory note should be added to the MBS item indicating that there is no restriction on the frequency of testing under specific circumstances (i.e. multiple testing is permitted in the case of a negative test result, but should not be used for other prognostic reasons). However, post-PASC, the department advised that such an explanatory note is unimplementable in practice as regardless of this note, the item would still be restricted by the descriptor (i.e. to once per primary tumour diagnosis). The department advised that the proposed item would allow providers to perform follow up tumour testing at their own discretion following an initial ctDNA test, but that this would only be covered by one rebate. PASC noted (out-of-session) from departmental advice that the explanatory note is unimplementable in practice and accepted that it is not required. PASC reasoned that if the concordance data regarding PIK3CA *testing in tumour tissue and ctDNA from INAVO120 trial (data forthcoming) demonstrates high concordance, then confirmatory testing is likely not required. If there was low concordance between tumour tissue and ctDNA results, confirmatory testing may be required. Therefore, PASC advised that while the current wording of the MBS item descriptor reflects the intent to provide testing once per primary tumour diagnosis, this wording may need to be updated to allow confirmatory follow up testing depending on the concordance data available. The department noted that, if the schedule fee adequately covers the costs of the services, including any potential subsequent retesting, this will support patients to access testing without any out-of-pocket expenses.*

In response to the applicant's enquiry at the pre-PASC stage, the Department responded that new items on the MBS are generally and preferably brand agnostic. Typically, the item descriptor would only name the biomarker required for access to the PBS drug.

The applicant suggested that *PIK3CA* testing costs $350-400 at several private and public molecular pathology laboratories. It was foreshadowed that an MBS fee of $350-400 will be proposed. However, the proposed MBS fee will be determined by the costing information gathered during the preparation of any forthcoming reimbursement submission. The applicant is currently engaging with molecular pathology laboratories to understand the costs associated with *PIK3CA* testing. The applicant anticipated $0 out-of-pocket expense as the proposed MBS fee will be in the same price range as the market *PIK3CA* testing fee.

Of note, a BC-focused gene panel test, which includes *AKT1, PIK3CA, ERBB2* and *ESR1*, using tumour tissue costs $375 at a laboratory in Australia (Sonic Genetics 2024).

PIK3CA testing in mBC patients is currently self-funded by patients or funded through State-based programs, at several private and public molecular pathology laboratories. *PIK3CA* testing may be performed through research funding or supported by the sponsor of clinical trials.

No MBS fee was proposed in the Ratified PICO of MSAC Application 1604 for a tumour test to detect *PIK3CA* variants for access to alpelisib.

There are no MBS items for ctDNA testing and hence no reference MBS fee can be obtained. Of note, analysis of tumour tissue for a single gene costs $340-400, based on MBS item 73374, 73379 and 73430.

PASC noted that there is currently no MBS funded PIK3CA *testing for either tumour tissue or ctDNA. PASC considered the proposed fee ($350-400) reasonable for single gene tumour tissue testing, based on the tumour tissue testing offered by a range of laboratories in Australia. However, PASC questioned the appropriateness of the fee for the overall application, considering ctDNA and tumour tissue testing may be costed differently. PASC considered that the fee for ctDNA is likely to be higher, as the testing method should be able to detect very low frequency variants in ctDNA.*

PASC noted from departmental advice that there is typically a preference to avoid listing different MBS item descriptors for the same service using different methodologies, meaning that ideally a single fee is proposed for both test types, but acknowledged exceptions apply.

*PASC noted from the PICO of MSAC Application 1766 that a multigene panel using tumour tissue to characterise three genes involving the AKT pathway (*PIK3CA, AKT1 *and* PTEN*) could potentially cost around $1000-$1200. PASC noted that this application is yet to be considered by MSAC.*

Of note, FoundationOne® Liquid CDx could be requested at a cost of $3,590 (as of July 2023 via Sonic Genetics), with a comprehensive genomic profiling of more than 300 genes, but it is unclear if the test is conducted and completed in Australia and hence, the eligibility for MBS funding is uncertain.

Summary of public consultation input

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

- Rare Cancers Australia (RCA)
- The National Pathology Accreditation Advisory Council (NPAAC)

The consultation feedback received from Rare Cancers Australia was supportive of public funding for genetic testing to detect *PIK3CA* mutations in patients with HR+/HER2- LA/mBC, to determine eligibility for treatment with PBS subsidised inavolisib.

The main benefits of public funding were access to genetic tests and targeted therapies providing more personalised and effective treatment options, improved quality of life, and financial and emotional relief to patients.

Rare Cancers Australia stated that patients often suffer from significant side effects, such as loss of appetite, lethargy and weight loss due to treatments and may endure mastectomies and the subsequent plastic surgeries required to correct surgical impacts. Rare Cancers Australia stated the financial cost of accessing therapy can lead patients to resort to selling their home, impacting the security, safety and financial stability of their family.

The NPAAC provided targeted input on the accreditation requirements for ctDNA. NPAAC stated that ctDNA is a new analyte in the Australian regulatory environment requiring a much lower limit of detection (LOD) in a test, that there are no NGS-based ctDNA tests listed on the ARTG and that testing is likely to be provided as an in-house developed assay. NPAAC also noted there is currently no RCPA quality assurance program for ctDNA to assess the pre-analytical process including stability of the sample and variable fractions of tumour DNA in circulation.

NPAAC advised that as of 2026 the TGA will require a new application to comply with amended regulations and that there may be TGA input into the accreditation of in-house tests and a requirement for tests to be validated against the reference assay used in the clinical trial.

Next steps

The applicant expected to submit a parallel, integrated codependent assessment report to MSAC and PBAC in February 2025.

Applicant Comments on Ratified PICO

The applicant had no comment.

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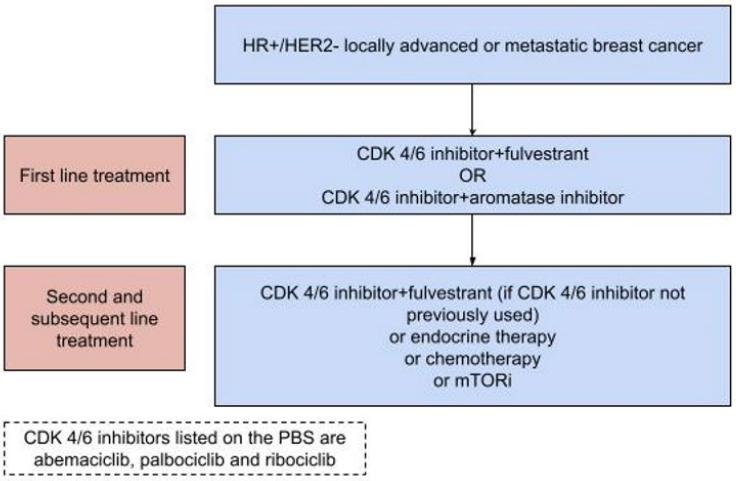
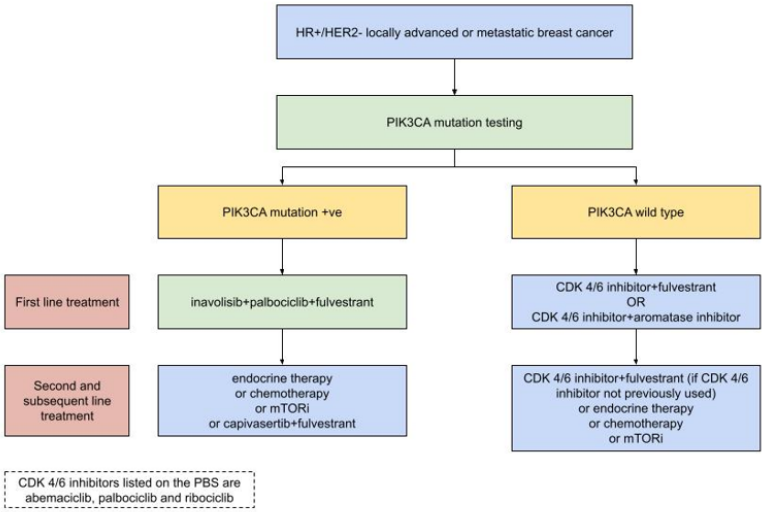
Appendix 1



Appendix Figure 5: Clinical management algorithm <u>without</u> *PIK3CA* testing and inavolisib.

Source: Figure 1, p13 of MSAC application 1783 PICO set



Notes: Green shaded boxes highlight proposed changes to current pathway. The outcome of PIK3CA mutation testing is highlighted in yellow.

Appendix Figure 6: Clinical management algorithm <u>with</u> *PIK3CA* testing and inavolisib

Source: Figure 2, p14 of MSAC application 1783 PICO set