MSAC application 1798

Liquid biopsy in patients with non-small cell lung cancer

Application for MBS eligible service or health technology

HPP Application number:

HPP200250

Application title:

Liquid biopsy in patients with non-small cell lung carcinoma

Submitting organisation:

HEALTH TECHNOLOGY ANALYSTS PTY LIMITED

Submitting organisation ABN:

13099239442

Application description

Succinct description of the medical condition/s:

Lung cancer is the fifth most-diagnosed cancer in Australia, with an estimated 14,714 new cases in 2023 (AIHW 2024). There are two main types of lung cancer, small cell (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is the more common, accounting for 85-90% of lung cancers (ACS 2024), and is the focus of this application. NSCLC is comprised of different subtypes, most commonly adenocarcinoma, followed by squamous cell carcinoma and large cell (undifferentiated) carcinoma (Cancer Australia 2024).
NSCLC can be further classified according to the presence of oncogenic alterations that affect tumour growth and invasiveness (Chevallier et al. 2021). It is estimated that over 65% of patients with advanced NSCLC have a targetable genomic alteration (Cheng et al. 2021) potentially as high as 80% in Asian populations (Tan and Tan 2022). Biomarker testing is indicated in advanced NSCLC to detect actionable driver alterations and thus inform appropriate treatment.

Succinct description of the service or health technology:

The proposed medical service is a liquid biopsy test, through the collection and analysis of circulating tumour DNA (ctDNA) from plasma isolated from whole blood samples, for the detection of oncogenic alterations in patients with NSCLC. The service is proposed to be used with next-generation sequencing (NGS) technology, enabling the detection of multiple oncogenes simultaneously according to a defined gene panel.

Application contact details

Are you the applicant, or are you a consultant or lobbyist acting on behalf of the applicant?

Consultant

Are you applying on behalf of an organisation, or as an individual?

Organisation

Applicant organisation name:

AstraZeneca

Daiichi Sankyo Australia

Illumina

SOPHiA Genetics

Thermo Fisher Scientific

Application details

Does the implementation of your service or health technology rely on a new listing on the Pharmaceutical Benefits Scheme (PBS) and/or the Prescribed List?

No

Is the application for a new service or health technology, or an amendment to an existing listed service or health technology?

New

Relevant MBS items

Please select any relevant MBS items.

MBS item number	Selected reason type

What is the type of service or health technology?

Investigative

Please select the type of investigative health technology

Molecular diagnostic tests

Please select the type of molecular diagnostics health technology:

Multigene/biomarker panel assay

Specify the number of genes/biomarkers in the panel assay:

>10 genes

Is it possible to vary or select the genes/biomarkers requested within the panel?

Yes

PICO sets

Application PICO set: Sequential testing

State the purpose(s) of the health technology for this PICO set and provide a rationale:

Purpose category:
Diagnosis / sub-classification
Purpose description:
To establish a diagnosis or disease (sub)classification in symptomatic or affected patients

Purpose category:
Predictive
Purpose description:
To provide predictive information to support selection of a specific therapy or intervention

Purpose category:
Prognosis
Purpose description:
To provide information about prognosis (staging/re-staging)

What additional purpose(s) could the health technology be used for, other than the purposes listed above for this PICO set?

Purpose category:
Monitoring

Purpose description:
To monitor a condition over time.
Rationale:
The use of liquid biopsy for minimal residual disease testing or treatment response monitoring is not within the scope of this application, due to insufficient evidence and lack of clear guidelines for routine adoption in practice at this time.

Purpose category:
Outcome/response assessment
Purpose description:
To assess an outcome or response following an intervention or treatment.
Rationale:
The use of liquid biopsy for minimal residual disease testing or treatment response monitoring is not within the scope of this application, due to insufficient evidence and lack of clear guidelines for routine adoption in practice at this time.

Population

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

This PICO set supports a request for MBS items for NGS-based gene panel testing using liquid biopsy in patients with NSCLC who cannot receive or have failed tissue-based gene panel testing. Patients unfit to undergo rebiopsy or who have insufficient tissue for molecular testing or failed tissue-based testing and require a rebiopsy have the highest clinical need for an additional testing method such as liquid biopsy. Note, this application does not propose liquid biopsy testing in patients with suspected lung cancer (i.e. before histopathological confirmation of NSCLC) and the proposed service is primarily intended to determine eligibility for PBS-listed targeted treatments. All targeted therapies currently listed on the PBS require confirmation of NSCLC diagnosis. As such, patients with suspected lung cancer who are medically unfit for tissue sampling for histopathological diagnosis would be unable to access PBS-listed medicines that require a NSCLC diagnosis even with a liquid biopsy test. While clinician feedback has indicated the utility of molecular testing in enhancing the diagnostic picture of a patient, the use of liquid biopsy for diagnosis of NSCLC is not supported by current guidelines or clinical evidence (Riely et al. 2024).
The proposed population is not restricted by NSCLC subtype. While molecular alterations are more common in non-squamous NSCLC, molecular profiling of squamous NSCLC has been found to be of value, particularly in light, or never-

smoking patients (Sands et al. 2020). In their evaluation of small gene panel tissue testing in NSCLC, the Evaluation Sub-committee (ESC) recognised that, although rarely reported, squamous cell carcinoma has several potentially targetable driver mutations (1721 Final PSD Nov 2022, p. 35), and advised that eligibility should not be restricted by subtype.

The proposed population also includes all patients with NSCLC irrespective of disease stage. While the NCCN Guidelines recommend testing in advanced or metastatic disease, the Applicant highlights the rapidly evolving clinical landscape for targeted therapies in early-stage NSCLC, given the recent approval of osimertinib for early-stage disease (AstraZeneca 2024), and increasing evidence supporting the use of new-generation tyrosine kinase inhibitors (TKIs) in early disease (Wu, Dziadziuszko, Ahn, et al. 2024). In addition, the NCCN Guidelines' recommendations on molecular testing in advanced or metastatic NSCLC apply to both plasma- and tissue-based molecular testing. Conversely, the MBS items for tissue-based multi-gene panel testing do not restrict eligibility according to disease stage.

Considering the above, this application requests that the eligible patient population for liquid biopsy mirrors that of the tissue-based panel test (MBS items 73437, 73438, 73439), to include patients diagnosed with NSCLC, without restriction by subtype or stage of disease.

Currently, tissue-based testing (multi-gene NGS panel or sequential single-gene testing) is funded on the Medicare Benefits Schedule (MBS) for NSCLC and considered standard of care for molecular testing in Australia. However, there remains an unmet need for an alternative means of molecular testing in patients who cannot have tissue-based testing. Tissue insufficiency is a limitation with tissue-based testing, where the patient may need to undergo a rebiopsy to complete molecular testing. Without molecular biomarker testing, patients cannot be assessed for eligibility for targeted therapies, whether via the Pharmaceutical Benefits Scheme (PBS) or in clinical trials.

A liquid biopsy is minimally invasive, requiring only a blood sample from the patient, and is therefore safer than tissue-based testing and has high patient acceptance. Liquid biopsy has clear utility as an alternative where tissue-based testing is not an option or to reduce the need for a rebiopsy. The NCCN Guidelines and the European Society for Medical Oncology (ESMO) guidelines recommend the use of liquid biopsy when the patient is medically unfit for invasive tissue sampling or if there is insufficient tissue for molecular analysis requiring a rebiopsy (Hendriks et al. 2023; Riely et al. 2024).

Patients unable to receive tissue-based testing currently choose to pay out-of-pocket

for testing via liquid biopsies, otherwise they receive no molecular testing if tissue is insufficient or unavailable. This means that liquid biopsies are limited to those who can afford the expense, contributing to inequitable healthcare access. Apart from cost considerations, geographic location can pose a significant barrier to accessing any testing, as the invasive tissue biopsy procedure is often only conducted at major hospitals in metropolitan areas. With MBS funding, liquid biopsy would provide a molecular testing option for patients who would otherwise require a rebiopsy and risk treatment delays, or not have the opportunity to be considered for effective life-extending treatments.

Select the most applicable Medical condition terminology (SNOMED CT):

Non-small cell lung cancer

Intervention

Name of the proposed health technology:

Liquid biopsy

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 health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

The current standard of care for biomolecular testing in NSCLC is tissue-based testing, which is the only publicly funded means of testing in Australia. This application proposes the use of liquid biopsy in patients with insufficient tissue for molecular testing who require a rebiopsy, or who fail tissue-based testing.

In newly diagnosed patients:

- For patients with insufficient tissue for molecular testing after diagnosis, or who fail tissue-based testing, and are unable to undergo tissue rebiopsy for medical reasons or who otherwise refuse, the comparator is no genetic testing.
- For patients with insufficient tissue for molecular testing after diagnosis, or who fail tissue-based testing, but are candidates for rebiopsy the comparator is rebiopsy followed by tissue-based multi-gene panel testing.

In the relapse setting, the main comparator is no molecular testing, as:

- The only test currently funded on the MBS in the relapse setting is single-gene testing for EGFR T790M for access to osimertinib on the PBS (MBS item no. 73351). EGFR T790M testing is only relevant as a comparator for patients with NSCLC who have progressed on or after first-line treatment with first- or second-generation EGFR TKIs such as erlotinib or gefitinib and are candidates for rebiopsy. Since osimertinib has been recommended for first-line treatment in EGFR-positive locally advanced or metastatic NSCLC, this test is rarely used (Medicare statistics indicate that this item was used only 20 times between June 2023 and June 2024).
- For the patients progressing on 1st or 2nd generation EGFR TKIs who are unable to undergo a tissue rebiopsy, or who fail the EGFR T790M test, the comparator is no molecular testing.

Outcomes

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

Patients not eligible for tissue biopsy are not eligible for PBS-listed targeted treatments. Liquid biopsy can identify additional patients with actionable alterations not detected by tissue biopsy. Thus, liquid biopsy results will increase allocation to appropriate treatment, and consequently improve overall patient health outcomes. In patients with insufficient tissue or who did not receive tissue testing (due to tissue not available or biopsy not possible), liquid biopsy was able to detect an actionable alteration in 17-40% of patients (Aggarwal et al. 2019; Mack et al. 2020; Park et al. 2021; Pritchett et al. 2019; Remon et al. 2019). Therefore, liquid biopsy results in up to 40% of patients being able to receive targeted therapy, who otherwise would not be identified/eligible.

Liquid biopsy also enables the avoidance of rebiopsy (and its associated risks) in patients with insufficient tissue following histopathological diagnosis (between 6.4% and 16.5% of cases) and in patients who fail tissue testing (between 12% to 38% of cases) (Aggarwal et al. 2019; Goswami et al. 2016; Gutierrez et al. 2017; Morris et al. 2018; Park et al. 2021; Pritchett et al. 2019; Raez et al. 2023; Remon et al. 2019; Sadik et al. 2022). Gutierrez et al. (2017) reported that 43% of patients with insufficient tissue for testing on the initial biopsy specimen underwent a second biopsy. Among patients with insufficient tissue for tissue NGS, the availability of liquid biopsy NGS testing resulted in only 13.3% of patients undergoing a repeat biopsy for tissue NGS with the remaining 82.7% of patients undergoing liquid biopsy (Li et al. 2021). In

addition, rebiopsies are associated with a 20% failure rate (1721 Final PSD Nov 2022). All patients who fail rebiopsy would currently receive non-targeted therapy. As noted above, up to 40% of these patients may potentially be eligible for targeted therapy with access to liquid biopsy testing.

- Test accuracy: Specificity, or NPA; Sensitivity, or PPA; Concordance, or OPA, test turnaround time, test success rate
- Change in patient management: Time to treatment initiation, change in treatment, rate of rebiopsy
- Test-related adverse events: Adverse events related to venous blood sampling
- Health outcomes: OS, PFS, Quality of life
- Healthcare system: Utilisation, Healthcare costs, Cost-effectiveness analysis, Total cost to MBS and PBS

Proposed MBS items

Proposed item:

AAAAA

Proposed category:

PATHOLOGY SERVICES

Proposed group:

GENETICS

Proposed item descriptor:

Characterisation of a variant or variants in a multi-gene panel using cell-free nucleic acid from plasma sample, requested by, or on behalf of, a specialist or consultant physician, to inform the clinical management of patient with NSCLC, in whom tissue testing is not an option or has failed.
Testing should include, but not be restricted to, actionable alterations as described in relevant international and/or local guidelines, such as EGFR, BRAF, KRAS, METex14sk, ERBB2 (HER2), ALK, ROS1, RET, NTRK1, NTRK2 and NTRK3.

Proposed MBS fee:

$3,000.00

Indicate the overall cost per patient of providing the proposed health technology:

$3,000.00

Please specify any anticipated out of pocket expenses:

$0.00

Provide any further details and explain:

The proposed fee:

- Accounts for the costs of specialised collection tubes, nucleic acid extraction, library preparation and sequencing, bioinformatics analysis, pathologist interpretation and reporting and pathology laboratory overheads, including the maintenance and service of instruments, data storage, quality assurance programmes, validation, rental and staffing.
- Covers the characterisation of the 11 genes specified in the proposed MBS items and provides scope for additional genes to be added as more targeted therapies become available on the PBS.
- Covers the necessary sequencing depth for a sufficiently high sensitivity assay
- Factors in the potential need for the assay to be run below maximum capacity.
- Ensures minimal or no out-of-pocket costs to the patient.
- Is benchmarked against the cost of homologous recombination deficiency (HRD) status testing, reimbursed at $3,000.00 (MBS item 73307) with respect to the level of sequencing and resources required.

Proposed item:

BBBBB

Proposed category:

PATHOLOGY SERVICES

Proposed group:

GENETICS

Proposed item descriptor:

A cell-free nucleic acid based multi-gene panel test of plasma sample of a patient with NSCLC, in whom tissue testing is not an option or has failed, requested by, or on behalf of, a specialist or consultant physician to detect variants which may include, but are not limited to, EGFR, BRAF, KRAS, METex14sk, ERBB2 (HER2), ALK, ROS1, RET, NTRK1, NTRK2 and NTRK3; and

a) to determine access to specific therapies relevant to these variants listed on the PBS; or

b) to determine if the requirements for access to immunotherapies listed on the PBS are fulfilled.

Proposed MBS fee:

$3,000.00

Indicate the overall cost per patient of providing the proposed health technology:

$3,000.00

Please specify any anticipated out of pocket expenses:

$0.00

Provide any further details and explain:

The proposed fee:

- Accounts for the costs of specialised collection tubes, nucleic acid extraction, library preparation and sequencing, bioinformatics analysis, pathologist interpretation and reporting and pathology laboratory overheads, including the maintenance and service of instruments, data storage, quality assurance programmes, validation, rental and staffing.
- Covers the characterisation of the 11 genes specified in the proposed MBS items and provides scope for additional genes to be added as more targeted therapies become available on the PBS.
- Covers the necessary sequencing depth for a sufficiently high sensitivity assay
- Factors in the potential need for the assay to be run below maximum capacity.
- Ensures minimal or no out-of-pocket costs to the patient.
- Is benchmarked against the cost of homologous recombination deficiency (HRD) status testing, reimbursed at $3,000.00 (MBS item 73307) with respect to the level of sequencing and resources required.

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

Research funding or self-funded

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)?

Superior

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

Following diagnosis:

- For patients with insufficient tissue for molecular testing, or who fail tissue-based testing, and are unable to undergo tissue rebiopsy for medical reasons or who otherwise refuse, liquid biopsy delivers superior effectiveness and non-inferior safety compared to no genetic testing, due to additional patients identified with an actionable alteration and able to access appropriate treatment.
- For patients with insufficient tissue for molecular testing, or who fail tissue-based testing, but are candidates for rebiopsy, liquid biopsy delivers superior effectiveness and safety compared to rebiopsy followed by tissue-based multi-gene panel testing, due to more patients identified with an actionable alteration and able to access appropriate targeted therapy and fewer rebiopsies required.

Upon progression on or after first-line treatment with first- or second-generation EGFR tyrosine kinase inhibitors, for patients who are unable to undergo a tissue rebiopsy, or who fail the EGFR T790M test, liquid biopsy offers superior effectiveness and safety compared to no molecular testing.

Estimated utilisation

Estimate the prevalence and/or incidence of the proposed population:

The proposed population eligible for liquid biopsy testing are patients with NSCLC for whom tissue biopsy is medically inappropriate, or who have failed tissue biopsy or tissue-based testing. Patients may require liquid biopsy testing at progression or relapse. These estimates are preliminary and will be further examined within the ADAR.

Newly diagnosed patients:

The projected incidence (new cases) of lung cancer in Australia in 2026 is 15,727 (AIHW 2023). It is estimated that NSCLC makes up around 86.6% of lung cancer (Mitchell et al. 2013).

A tissue biopsy is required for pathological diagnosis and to obtain a sample for molecular testing, but literature estimates that 20% of patients are medically unfit to

undergo the procedure (Bosc et al. 2015; Chouaid et al. 2014; Murray et al. 2012; Trédan et al. 2019), and consultation with Australian KOLs corroborate this estimate. As liquid biopsy is not proposed to be used in a diagnostic capacity, the proposed use of liquid biopsy is limited to the newly diagnosed patient population confirmed by tissue histology and not in patients unable to have a confirmative tissue biopsy. As previously discussed, genetic alterations are commonly associated with non-squamous NSCLC subtype, demonstrating a requirement for multi-gene testing within this patient population, which is around 80% of all NSCLC (Tissera et al. 2022). Additionally, alterations are also associated with patient factors such as young age (less than 50 years) which make up around 4% (Tissera et al. 2022) and a history of no tobacco exposure, which make up 20% of all lung cancer cases (Institute for Respiratory Health 2023; Tissera et al. 2022). Patients with NSCLC of squamous subtypes fitting these criteria are more likely to harbour genetic alterations, and a specialist may request genetic testing if this is suspected. It is assumed that patients who receive tissue testing receive a small gene panel test (MBS item: 73437). The panel has a reported 3% failure rate (1721 PSD small gene panel). Patients who experience tissue testing failure can forgo having a re-biopsy and will be eligible for liquid biopsy instead. Additionally, patients who receive a tissue biopsy for diagnosis may have insufficient tissue for tissue-based NGS testing but would be eligible for liquid biopsy. This is estimated to be around 13% of patients (Gutierrez et al. 2017). The estimated total number of patients with newly diagnosed NSCLC eligible for liquid biopsy is 1,563 patients.

Patients relapsing on treatment:
The projected population in 2026 in Australia is 28.4M (Australian Bureau of Statistics 2018). Applying the calculated crude prevalence rate of lung cancer (0.15%) and proportion of patients with NSCLC (86.6%) it is estimated that 35,841 Australians will be living with NSCLC in 2026. Recent data suggest that around 9% of all NSCLC patients are treated with targeted therapy 1L (Roberts et al. 2023) however, given the recent approval of osimertinib for early-stage disease (AstraZeneca 2024), and increasing evidence supporting the use of new-generation targeted therapies in early disease (Wu, Dziadziuszko, Ahn Jin, et al. 2024), this data is unlikely to be representative of current practices. Input from KOLs estimate this figure to be closer to 25-30% of patients. In a real-world study, Bauman et al. (2024) found that around 24-41% (median: 33%) of patients (with ALK mutation) receiving 1L TKI never received any 2L treatment due to clinical deterioration. Of the remaining patients, KOL input suggests that around 50% of these patients would require further

biomarker testing to check for acquired resistance alterations.
However, KOLs estimate around only 25% of progressing patients can undergo tissue biopsy procedures due to deteriorating health. These patients are eligible to undergo a liquid biopsy as a standalone test.
The estimated total number of patients with NSCLC eligible for liquid biopsy at relapse is 2,272 patients.

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake (%):

20

Year 2 estimated uptake (%):

28

Year 3 estimated uptake (%):

40

Year 4 estimated uptake (%):

57

Estimate the number of patients who will utilise the proposed technology for the first full year:

767

Optionally, provide details:

Uptake is dependent upon the availability of accredited laboratories offering NGS-based genotyping of ctDNA using liquid biopsy. An attachment is provided listing laboratories in Australia that are currently accredited or seeking accreditation by NATA to provide liquid biopsy services. We approximate that uptake in year one is around 20%. Real world data from the US and Europe show that 80-85% of patients with non-squamous NSCLC will receive any biomarker testing (European Society for Medical Oncology 2022; Evangelist et al. 2024), and we assume that uptake will reach this maximum rate at year 5.
These figures are our best estimates at this time and are subject to change if additional targeted therapies become available on the PBS and/or there are increases in the number of accredited laboratories able to offer the liquid biopsy service.

Will the technology be needed more than once per patient?

Yes, multiple times

Over what duration will the health technology or service be provided for a patient? (preferably a number of years):

As clinically relevant over the course of disease.

Optionally, provide details:

The proposed test is applicable once per diagnostic episode, at diagnosis or at disease progression on or after treatment. Similar to tissue-based NGS testing (MBS item 73437, 73438, 73439), the test should not be repeated unless deemed clinically relevant, for example, at the development of a new tumour or upon further advancement of disease that is considered to change the likelihood of biomarker detection via liquid biopsy.
Note, the use of liquid biopsy for minimal residual disease testing or treatment response monitoring is not within the scope of this application.

What frequency will the health technology or service be required by the patient over the duration? (range, preferably on an annual basis):

N/A

Optionally, provide details:

The proposed test is applicable once per diagnostic episode, at diagnosis or at disease progression on or after treatment. Similar to tissue-based NGS testing (MBS item 73437, 73438, 73439), the test should not be repeated unless deemed clinically relevant, for example, at the development of a new tumour or upon further advancement of disease that is considered to change the likelihood of biomarker detection via liquid biopsy.
Note, the use of liquid biopsy for minimal residual disease testing or treatment response monitoring is not within the scope of this application.

Consultation

List all entities that are relevant to the proposed service / health technology. The list can include professional bodies / organisations who provide, request, may be impacted by the service/health technology; sponsor(s) and / or manufacturer(s) who produce similar products; patient and consumer advocacy

organisations or individuals relevant to the proposed service/health technology.

Entities who provide the health technology/service:

Royal College of Pathologists of Australasia (RCPA)

Australian Pathology

Human Genetics Society of Australasia

Entities who request the health technology/service:

The Medical Oncology Group of Australia (MOGA)

Thoracic Oncology Group of Australasia (TOGA)

Clinical Oncology Society of Australia (COSA)

Private Cancer Physicians of Australia (PCPA)

Australian & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS)

Thoracic Society of Australia and New Zealand (TSANZ)

Royal College of Pathologists of Australasia (RCPA)

Entities who may be impacted by the health technology/service:

The Medical Oncology Group of Australia (MOGA)

Thoracic Oncology Group of Australasia (TOGA)

Clinical Oncology Society of Australia (COSA)

Australian & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS)

Thoracic Society of Australia and New Zealand (TSANZ)

Royal College of Pathologists of Australasia (RCPA)

Australian Pathology

Human Genetics Society of Australasia

Australian Genomics

Pathology Technology Australia

Patient and consumer advocacy organisations relevant to the proposed service/health technology:

Lung Foundation Australia

Rare Cancers Australia

Regulatory information

Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?

Yes

Has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

No

Is the therapeutic good classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

Class III

Is the therapeutic good to be used in the service exempt from the regulatory requirements of the Therapeutic Goods Act 1989?

No

Is the therapeutic good classified by the TGA as for Research Use Only (RUO)?

Yes