MSAC Application 1798

Liquid biopsy in patients with non-small cell lung cancer

PICO Set

Population

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

This PICO set supports a request for Medicare Benefits Schedule (MBS) items for gene panel testing using liquid biopsy in patients with non-small cell lung cancer (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 a high unmet clinical need for an additional testing method such as liquid biopsy.

Disease overview

Lung cancer is the fifth most-diagnosed cancer in Australia, with an estimated 14,714 new cases in 2023 (AIHW 2024). Tobacco smoke exposure remains the greatest risk factor for lung cancer, but the impact of environmental risk factors, such as exposure to second-hand smoke and air pollution is substantial. It has been reported that 20% of Australians with lung cancer have never smoked (Institute for Respiratory Health 2023). While the incidence of lung cancer rates in Australia is projected to fall in the next two decades, the proportion of never-smokers diagnosed with lung cancer has risen in many countries (Barta et al. 2019).

There are two main types of lung cancer, classified by the size of cancer cells seen under a microscope, small-cell lung cancer (SCLC) and NSCLC. NSCLC accounts for around 85-90% of lung cancers total (ACS 2024) making it the most common type of lung cancer. Most recent statistics indicate the 5-year survival rate of NSCLC in Australia for Stage 3 disease is 24%, reducing to 10% for Stage 4 disease (Denton et al. 2016). Lung cancers such as NSCLC generally have a poor prognosis and are the leading cause of cancer-related deaths in Australia and world-wide (AIHW 2023a; Chevallier et al. 2021). Mortality caused by lung cancer is expected to increase despite the reduction in tobacco consumption, with an increasing population and life expectancy (AIHW 2023b; Chevallier et al. 2021).

NSCLC is comprised of different subtypes (Cancer Australia 2024), most commonly:

- Adenocarcinoma, which originates in the mucus-secreting cells in the deeper part of the lungs. The commonest form of non–small cell lung cancer, including in non-smokers and younger people.
- Squamous cell carcinoma, which originates in the cells lining the airways of the lungs, usually close to a main airway.
- Large cell (undifferentiated) carcinoma, which can originate in several types of cells. Small-cell lung cancer tends to grow and spread quickly. It has usually spread to other parts of the body before it is detected.

The subtype of NSCLC is often a prognostic factor. For example, squamous cell carcinoma is associated with a better prognosis in resected patients whereas adenocarcinoma has a better prognosis in advanced NSCLC (J. Bosch-Barrera et al. 2012). Critically, the subtype of NSCLC informs treatment choice, allowing regimens to be tailored for response to treatment (Selvaggi and Scagliotti 2009).

The NSCLC subtype is only one of the factors influencing clinical management. NSCLC is recognised as a complex and heterogeneous disease (Levine and Weisberger 1955). It 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 greater than 65% of patients with advanced NSCLC have a targetable genomic alteration (Cheng et al. 2021) and potentially as high

as 80% in Asian populations (Tan and Tan 2022). Genetic alterations are mostly found in lung adenocarcinoma, commonly in *EGFR*, *ALK* and *ROS1* genes, and are least reported in lung squamous cell carcinoma (Cancer Genome Atlas Research Network 2014). Different genetic alterations also arise from lifestyle factors; smokers and non-smokers often have biologically distinct tumours (Dubin and Griffin 2020). This diversity in genetic profiles is an important attribute influencing treatment decisions and impacting prognosis. *KRAS* alterations are most common in NSCLC and are most aggressive and refractory to treatment (Julian et al. 2023). Within *EGFR* alterations, exon 20 insertions have a worse prognosis compared to classical *EGFR* alterations like exon 19 deletions and exon 21 L858R substitutions (Oxnard et al. 2013).

Tumour genetic heterogeneity can also be observed within individual patients, as different tumour sites can vary in molecular characteristics. Differences may be observed between different parts of a given tumour, between tumour sites or between the primary tumour and metastases (spatial heterogeneity) (Zhu et al. 2021). Differences may also be observed over time due to tumour evolution such as may be seen with recurrent or metastatic disease (temporal heterogeneity) (Zhu et al. 2021). Intra-patient tumour heterogeneity has implications for diagnosis, prognosis and treatment, but is challenging to evaluate based on a tumour biopsy that is limited to single site (Zhu et al. 2021).

The identification of the presence or absence of specific biomarkers offers predictive value that informs treatment choice with either targeted or non-targeted therapies. The 2024 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for NSCLC recommend initial PD-L1 expression testing in patients with metastatic NSCLC to assess whether patients are candidates for immune checkpoint inhibitors (ICIs), as well as molecular testing for actionable genetic variants including *ALK*, *BRAF*, *EGFR*, *ERBB2* (*HER2*), *KRAS*, *METex1sk*, *NTRK1*, *NTRK2*, *NTRK3*, *RET*, and *ROS1* variants (Riely et al. 2024). If molecular testing results are unknown or pending, then patients are treated as though they do not have driver oncogenes (Riely et al. 2024). Targeted therapies with a first-line indication are recommended as initial therapy (rather than first-line ICIs) for patients with some (but not all) oncogenic drivers, regardless of PD-L1 levels, because targeted therapies yield higher response rates than ICIs in the first-line setting and are better tolerated (Riely et al. 2024). NSCLC patients with oncogenic alterations often respond poorly to immunotherapy, and patients with *EGFR* mutation yielded a lack of overall survival benefit when treated with immunotherapy compared to chemotherapy (HR 1.11; 95% CI, 0.80-1.53) (McLean et al. 2021), further highlighting the importance of appropriate targeted therapies. Patients without targetable genomic alterations are recommended to receive chemotherapy plus immunotherapy (Riely et al. 2024). Table 1 outlines the oncogenic drivers in NSCLC that can be therapeutically targeted with treatments currently available in Australia.

Table 1 Market status of targeted therapies in Australia

Variant	Prevalence	Targeted therapy	ARTG status	PBS listing
EGFR	19.2%	Erlotinib, gefitinib, afatinib, osimertinib	Registered	Listed
ALK	3.8%	Crizotinib, alectinib, brigatinib, ceritinib, lorlatinib	Registered	Listed
ROS1	2.6%	Crizotinib, entrectinib	Registered	Listed
METex14sk	3%	Tepotinib	Provisional registration	Listed
NTRK	0.23%	Larotrectinib	Provisional registration	Listed
BRAF	2.1%	Dabrafenib, trametinib	Registered	Not listed
KRAS	25.3%	Sotorasib	Provisional registration	Not listed
RET	1.7%	Pralsetinib, selpercatinib	Provisional registration	Recommended by PBAC
ERBB2 (HER2)	2.3%	Trastuzumab deruxtecan (2L), Ado-trastuzumab emtansine (2L)	Not registered in NSCLC	Not listed
EGFR T790M	50-60% of EGFR TKI acquired resistance	Osimertinib	Registered	Listed

Source: John et al., 2020; Tan & Tan, 2022; Farago et al., 2018; Rolfo et al., 2021; www.mbsonline.gov.au; www.pbs.gov.au; www.tga.gov.au/resources/artg
Abbreviations: *ALK*, anaplastic lymphoma kinase; ARTG, Australian Register of Therapeutic Goods; *BRAF*, v-raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma viral oncogene; *METex14sk*, mesenchymal-epithelial transition exon 14 skipping; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; PBS, Pharmaceutical Benefits Scheme; *RET*, rearranged during transfection; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase; T790M, Thr790Met, methionine for threonine at amino acid position 790; TGA, Therapeutic Goods Administration; TKI, tyrosine kinase inhibitor

While most of the above treatments are registered in Australia for use in advanced NSCLC, it should be noted that osimertinib has recently been granted TGA approval for use in early-stage NSCLC (AstraZeneca 2024), and there are many other ongoing studies exploring targeted therapy use in early-stage disease. In anticipation of the rapidly evolving treatment landscape, the proposed liquid biopsy testing of patients is not restricted by stage of disease. Furthermore, testing can reduce inappropriate treatment and determine patient eligibility for participation in clinical trials. ASCO guidelines maintain the view that clinical trials are vital in improving cancer care and all patients should have the opportunity to participate (Singh et al. 2023).

Sequential testing

As outlined in Table 1, several targeted therapies are registered on the ARTG for NSCLC patients with an actionable genetic alteration. Evidence of the specific genetic alteration in tumour material is a requirement to access the relevant targeted therapy on the Pharmaceutical Benefits Scheme (PBS). Currently, tissue-based testing (multi-gene next-generation sequencing (NGS) panel or sequential single-gene testing) is funded on the 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.

All relevant global guidelines acknowledge that there are limitations to tissue testing which circulating tumour deoxyribonucleic acid (ctDNA) can overcome. Tissue insufficiency is a limitation with tissue-based testing, where the patient may need to undergo a rebiopsy to

complete molecular testing, which may not be feasible or safe in some patients. Quantity not sufficient (QNS) rates of between 6.4% and 16.5% have been reported for lung cancer (Goswami et al. 2016; Gutierrez et al. 2017; Morris et al. 2018; Sadik et al. 2022). Patients unable to undergo molecular biomarker testing successfully are not eligible for targeted therapies, whether via the PBS or in clinical trials. These patients are managed as if no genetic alterations exist and treated with standard of care, encompassing a combination or selection of treatments ranging from chemotherapy, radiation, immunotherapy, and biologics depending on patient eligibility.

Common complications associated with tissue biopsy of the lung include pneumothorax (12-45%), and haemorrhage (8-65%) (Stone and Fong 2023). In rare cases, death has also been reported with lung biopsies (Freund et al. 2012). 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 and 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 the need for 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 liquid biopsies, otherwise they receive no molecular testing if tissue is insufficient or unavailable. This means that liquid biopsies are currently 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. A liquid biopsy is simple to perform and can fulfil a clinical need in patients living in rural, regional and remote areas and provide equitable access to genetic testing. 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.

These populations (i.e. patients either unfit to undergo rebiopsy or who have insufficient tissue for molecular testing or failed tissue testing and require a rebiopsy) have the highest clinical need for an additional testing method such as liquid biopsy.

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

Following the initial symptomatic presentation to a general practitioner (GP), the patient is referred for a chest X-ray followed by a chest computed tomography (CT) scan and specialist referral if further investigation is warranted. An urgent chest CT scan and specialist referral may be ordered if there is a high suspicion of cancer upon initial presentation to the GP (Cancer Council 2021). The diagnosis of NSCLC is made upon tissue biopsy and imaging, aimed to be complete within 2 weeks of specialist referral. After diagnosis, the cancer is staged using positron emission tomography (PET)-CT and a biopsy of lymph nodes and/or metastatic sites. Once diagnosis and staging are complete, molecular biomarker testing may be warranted to inform treatment (Cancer Council 2021).

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 not be able 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).

This application requests that the eligible patient population for liquid biopsy includes patients diagnosed with NSCLC, without restriction by subtype or stage of disease.

Provide a rationale for the specifics of the eligible population:

The proposed population for liquid biopsy in this application is not restricted by NSCLC subtype. While genetic alterations are more commonly found in non-squamous NSCLC (Cancer Genome Atlas Research Network 2014)r, 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) also recognised that, although rarely reported, squamous cell carcinoma has several potentially targetable driver mutations, and thus advised that eligibility for the tissue-based panel test should not be restricted by subtype (1721 Final PSD Nov 2022, p. 35).

The proposed population also includes all patients with NSCLC irrespective of disease stage. While the current NCCN Guidelines recommend testing specifically for patients with 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 targeted therapies in early disease (Wu et al. 2024). Moreover, it is emphasised that the NCCN Guidelines' recommendations on molecular testing in advanced or metastatic NSCLC apply to both plasma- and tissue-based molecular testing. Equally, 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.

It is noted that the use of liquid biopsy for minimal residual disease testing or treatment response monitoring is not within the scope of this application.

In the relapse setting, the only MBS item currently available is single-gene testing for *EGFR T790M* for access to osimertinib on the PBS (MBS item no. 73351). It should be noted since osimertinib was listed as a first-line treatment in *EGFR*-positive locally advanced or metastatic NSCLC this test is not used as often (Medicare statistics indicate that this item was used only 20 times between June 2023 and June 2024). Thus, *EGFR T790M* testing is only relevant for patients with NSCLC who have progressed on or after first-line treatment with first- or second-generation

EGFR tyrosine kinase inhibitors such as erlotinib or gefitinib. The proposed population eligible for liquid biopsy in the relapse setting includes patients who have failed *EGFR T790M* testing.

Are there any prerequisite tests? (please highlight your response)

Yes No

Are the prerequisite tests MBS funded? (please highlight your response)

Yes No

Please provide details to fund the prerequisite tests:

Before a liquid biopsy testing for genomic profiling, the patient must have been diagnosed with NSCLC. It is not expected that there will be any changes in the prerequisite tests (Table 2) as a result of the proposed medical service.

Table 2 MBS items for prerequisite tests

MBS item	Procedure
61529	Whole body FDG PET study, performed for the staging of proven non-small cell lung cancer, where curative surgery or radiotherapy is planned (R)
38417	Endobronchial ultrasound guided biopsy or biopsies (bronchoscopy with ultrasound imaging, with or without associated fluoroscopic imaging) to obtain one or more specimens by: a) transbronchial biopsy or biopsies of peripheral lung lesions; or b) fine needle aspirations of one or more mediastinal masses; or c) fine needle aspirations of locoregional nodes to stage non-small cell lung carcinoma; other than a service associated with a service to which an item in Subgroup 1 of this Group, item 38416, 38420 or 38423, or an item in Subgroup I5 of Group I3, applies
38416	Endoscopic ultrasound guided fine needle aspiration biopsy or biopsies (endoscopy with ultrasound imaging) to obtain one or more specimens from either or both of the following: a) mediastinal masses; b) locoregional nodes to stage non-small cell lung carcinoma; other than a service associated with a service to which an item in Subgroup 1 of this Group, or item 38417 or 55054, applies

Source: www.mbsonline.gov.au

Intervention

Name of the proposed health technology:
Liquid biopsy

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

Genetic profiling using liquid biopsy-based NGS

A liquid biopsy can be performed on various bodily fluids such as saliva or urine, however, the proposed test is for the detection of actionable oncogenic alterations found in plasma isolated from blood. The use of blood and plasma for liquid biopsy is the most researched to date (Lockwood et al. 2023) and most appropriate as blood is most in contact with tumours. Tumour deposits shed circulating tumour DNA into the blood, which can be extracted and genotyped (Haber and Velculescu 2014).

The collection of specimens for biomarker analysis with liquid biopsy differs from that of a tissue biopsy. The proposed liquid biopsy is a minimally invasive procedure that uses standard veinous blood sampling for sample collection. On average, only 4-10ml of blood is required (Lockwood et al. 2023) and specialised collection tubes with additives that stabilise blood cells and prevent lysis should be used to prevent interference with the analysis (Hasenleithner and Speicher 2022). Following the collection of a blood sample, the plasma is isolated by centrifugation followed by extraction of cell-free DNA (cfDNA) by isolation methods (such as silica membrane-based spin columns, magnetic bead-based) (Hasenleithner and Speicher 2022; Lopez-Rios et al. 2023). The ctDNA is then ready to be sequenced and analysed.

Various molecular technologies can be applied for genotyping ctDNA (Rolfo et al. 2021). The applicant proposes the use of NGS technology to detect multiple genetic alterations in parallel against a specified gene panel. NGS offers better clinical utility than single-gene methods. Guidelines recommend molecular testing via a broad, panel-based approach like NGS where feasible (Riely et al. 2024). NGS-based genotyping of ctDNA from liquid biopsy is available in several National Association of Testing Authorities (NATA)-accredited laboratories in Australia.

Guidelines recommendations for biomarker testing in NSCLC

Oncogenic alterations recommended for routine testing in relevant international guidelines are presented in Table 3. The 2024 NCCN Guidelines recommend complete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1, NTRK2, NTRK3, METex14sk, RET, and ERBB2 (HER2) via biopsy and/or plasma testing, which may include concurrent or sequential combination testing approaches (Riely et al. 2024). The ERBB2 (HER2) genetic alteration recommended within routine screening according to the 2024 NCCN Guidelines has not yet been reflected in other guidelines by ESMO and IALSC. It should be highlighted that relevant guidelines are continually evolving to reflect the growing evidence for biomarker targets and available treatments.

Table 3 Summary of international guidelines on biomarker testing in NSCLC

Guideline	Target mutation	Methodology
Newly diagnosed		
CAP/IASLC/AMP 2018	Recommended: *EGFR*, *ALK*, *ROS1* Expert consensus (initial or after *EGFR*, *ALK*, *ROS1* negative): *RET*, *METex14sk*, *ERBB2* (*HER2*), *KRAS*, *BRAF*	PCR/NGS (*EGFR*), IHC ±FISH (*ALK*), IHC ± FISH/PCR/NGS (*ROS1*), NGS (*RET*, *METex14sk*, *ERBB2* (*HER2*), *KRAS*, *BRAF*)
ESMO 2023[1]	Recommended: *EGFR* (exons 19-21), or at a minimum, exon 19 deletion, exon 21 L8584 mutation, *ALK*, *ROS1*, *RET*, *METex14sk*, *NTRK*, *ERB2* (*HER2*), *KRAS*, *BRAF*	NGS (*EGFR*), RNA NGS; IHC ± molecular confirmation (NGS, FISH) (*ALK*), RNA NGS; IHC may be used for screening but molecular confirmation essential (NGS, or FISH) (*ROS1*), DNA/RNA NGS (*RET*, *METex14sk*, *NTRK*, *ERB2* [*HER2*], *KRAS*, *BRAF*)
NCCN 2024[2]	Recommended: *EGFR*, *ALK*, *KRAS*, *ROS1*, *BRAF*, *NTRK1*, *NTRK2*, *NTRK3*, *METex14sk*, *RET*, *ERBB2* (*HER2*)	NGS
Relapsed on targeted therapy		
CAP/IASLC/AMP 2018	Recommended: *EGFR T790M*	PCR/NGS
ESMO 2023[1]	Recommended: *EGFR T790M*, *MET*	PCR/NGS/FISH
NCCN 2024[2]	Recommended: *EGFR T790M*	NGS

Sources: Lindeman et al. (2018), Lindeman et al. (2013), Hendriks et al. (2023), Riely et al. (2024)
Abbreviations: *ALK*, anaplastic lymphoma kinase, AMP, Association for Molecular Pathology; *BRAF*, v-raf murine sarcoma viral oncogene homolog B; CAP, College of American Pathologists; DNA, deoxyribonucleic acid; *EGFR*, epidermal growth factor receptor; ERBB2, Erb-B2 Receptor Tyrosine Kinase 2; ESMO, European Society for Medical Oncology; FISH, fluorescence in situ hybridisation; HER2, human epidermal growth factor receptor 2; IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry; *KRAS*, Kirsten rat sarcoma viral oncogene; *METex14sk*, mesenchymal-epithelial transition exon 14 skipping; NCCN, National Comprehensive Cancer Network; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; PCR, polymerase chain reaction; *RET*, rearranged during transfection; RNA, ribonucleic acid; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase; T790M, Thr790Met, methionine for threonine at amino acid position 790
1 Grade A indicated mandatory testing.
2 Category 1 recommendations indicate uniform NCCN consensus (at least 85% of the NCCN Member Institutions on the panel) that the intervention is appropriate based on high-level evidence, such as randomised phase 3 trials. Also available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Current MBS items for biomarker testing

As of 01 November 2023, three MBS items for small gene panel sequencing (NGS) of tissue are listed for NSCLC. The current MBS items (73437, 73438, 73439) cover nucleic acid variant testing in *EGFR*, *BRAF*, *KRAS*, *MET* exon 14 genes and ribonucleic acid (RNA) fusion status of *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK2* and *NTRK3* genes (MBS 2023). An overview of corresponding targeted therapies available on the PBS for these variants is presented in Table 1.

Proposed intervention

The proposed intervention is the brand-agnostic NGS panel testing of cell-free nucleic acid from plasma for the detection of oncogenic alterations. The scale of gene analysis proposed is informed by international guidelines. While not all guideline-recommended genes have targeted treatments currently listed on the PBS, broad genotyping provides valuable information to help guide clinical management. In the listing of the current tissue NGS panel MBS item, it is of note that consideration of relevant future biomarkers was incorporated into the decision to list *KRAS*, *BRAF*, *METex14sk*, *RET*, and *NTRK1*, *NTRK2* and *NTRK3* in the MBS item, before the availability of targeted therapies in Australia.

Aligned with the NCCN Guidelines, the proposed item suggests the testing of *EGFR*, *BRAF*, *KRAS*, *METex14sk*, *ERBB2* (*HER2*), *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK2* and *NTRK3* genes. Thus, the proposed panel would include >10 genes. The Applicant recognises that the panel of genes and abnormalities detected with NGS will vary depending on the design and validation of the NGS

platform. Assays used with liquid biopsy may test for mutations and/or gene fusions at the DNA level, RNA level, both or not at all. While RNA-based panels for tissue biopsies are recognised to have better sensitivity and accuracy in detecting gene fusions compared to DNA-based panels, cell-free RNA (cfRNA) currently remains challenging to clinically validate (Bruno and Fontanini 2020; Heydt et al. 2021). It is the intention of the Applicant that the proposed MBS item reflects guideline-recommended genotyping, while recognising that not all NGS-based assays currently available in Australia will offer the ability to analyse all fusion genes, whether at the DNA or RNA level. Thus, the proposed item should not impose the minimal inclusion of these genes in the panel as a funding requirement.

In recognition of both the current treatment landscape and the shifting treatment paradigm, the primary proposed MBS item (option A) requests liquid biopsy testing for any of the variants recommended in international guidelines to inform the clinical management of a patient with NSCLC. This aligns closely with international guidelines and offers the clinical benefit of testing for a wider range of biomarkers as well as additional information provided by liquid biopsy around prognosis and tumour heterogeneity. MBS item (option A) is also anticipatory of targeted treatments that may become available in the near future. This proposed MBS item is thus comprehensive, holistic and future proof, aligned with the rapidly evolving landscape and continuous revision of international guidelines for molecular biomarker testing.

An alternative MBS item (option B) is also proposed, closely aligned with the currently available MBS items (73437, 73438, 73439) for tissue-based molecular testing in NSCLC. This MBS item requests liquid biopsy testing for *EGFR*, *BRAF*, *KRAS*, *METexon14sk*, *ERBB2* (*HER2*), *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK2* and *NTRK3* to determine access to appropriate therapies listed on the PBS.

Identify how the proposed technology achieves the intended patient outcomes:

As described above, heterogeneous tumour alterations within a patient are challenging to evaluate based on tissue sampling from a single biopsy site. In comparison, ctDNA represents a mix of DNA released by multiple tumour sites, capturing heterogeneity and therefore giving a better description of the genomic landscape that characterises the patient's cancer (Pascual et al. 2022). This enables a more holistic and comprehensive approach to clinical decision making.

The availability of liquid biopsy also addresses the treatment gap for those who are unable to have or fail tissue biopsy, with no alternative to biomarker testing. The clinical utility of a liquid biopsy is gained from the subsequent change in clinical management of a patient, increasing the proportion of patients receiving appropriate targeted therapy.

A liquid biopsy is less invasive than a tissue biopsy, with fewer associated adverse events. Common complications associated with tissue biopsy of the lung include pneumothorax (12-45%), and haemorrhage (8-65%) (Stone and Fong 2023). In rare cases, death has also been reported with lung biopsies (Freund et al. 2012). In comparison, a liquid biopsy only requires a standard venous blood sample, carrying a significantly lower risk of complications. Given these factors, a liquid biopsy has a high patient acceptance rate and can result in the avoidance of a rebiopsy and its associated complications.

Does the proposed health technology include a registered trademark component with characteristics that distinguish it from other similar health components? (please highlight your response)

Yes No

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

N/A

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

Yes No

Provide details and explain:

The service should be pathologist determinable in order to provide definitive diagnosis/classification.

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

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

Testing would be requested by the treating clinician and provided by an approved pathology practitioner in line with other tests in the MBS Pathology Services Table.

A venipuncture and venous blood sample is required for plasma-based NGS testing. Any appropriately trained medical professional will be able to collect a blood sample.

NGS testing should be conducted, and the results interpreted by suitably qualified and trained molecular pathologists. Testing should be conducted in specialist laboratories holding the appropriate accreditation i.e NATA and registration for this diagnostic procedure. The results should be interpreted and reported by suitably qualified and trained pathologists.

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

N/A

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

Patients should be referred by a respiratory specialist, oncologist or consultant physician.

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

Yes No

Provide details and explain:

Testing would be delivered by approved pathology practitioners with appropriate scope of practice in accredited pathology laboratories (as defined in the MBS Pathology Services Table) following referral by registered medical practitioners (non-pathologists) in line with other tests in the MBS Pathology Services Table.

Protocols and standards specified by NATA-accredited laboratories for blood collection, processing, storage and transport should be followed to ensure consistent quality of testing. cfDNA collecting tubes containing preservatives that preserve and stabilise the cell integrity of blood samples should be used. Liquid biopsy-based NGS would be conducted by NATA-accredited laboratories and the results interpreted and reported by suitably qualified and trained pathologists.

Indicate the proposed setting(s) in which the proposed health technology will be delivered: (select all relevant settings)

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

N/A

Is the proposed health technology intended to be entirely rendered inside Australia? (please highlight your response)

Yes No

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

N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian 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 and require a rebiopsy, or who fail tissue-based testing. The comparators are no molecular testing or rebiopsy followed by tissue-based multi-gene panel 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 molecular 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.

- 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 was listed as a 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.

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

Tissue-based multi-gene panel tests: 73437, 73438 and 73439.

EGFR T790M test: 73351

Please provide a rationale for why this is a comparator:

Tissue-based NGS panel testing is the current standard of care for genetic testing at diagnosis, while single-gene testing for *EGFR T790M* is the only test currently funded on the MBS in the relapse setting. Patients with insufficient tissue for testing following diagnosis would undergo a rebiopsy to obtain a further sample. If patients are unable to undergo tissue rebiopsy, there is no current alternative for molecular testing.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

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

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

Eligible patients will receive a liquid biopsy as an alternative to no genetic testing to determine access to targeted treatment for patients with an actionable alteration. Patients without an actionable mutation will continue to receive standard of care (chemotherapy, radiotherapy, immunotherapy etc.).

Outcomes

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

☒ Health benefits
☒ Health harms
☒ Resources
☐ Value of knowing

Outcome description – 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 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 who experienced tissue testing failure due to 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.

<u>Test accuracy</u>

- Specificity, or Negative Percent Agreement (NPA)
- Sensitivity, or Positive Percent Agreement (PPA)
- Concordance, or Overall Percent Agreement (OPA)
- Test turnaround time
- Test success rate

<u>Change in patient management</u>

- 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

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

Currently, there is no government funding for liquid biopsy-based NGS testing for actionable alterations in patients with NSCLC. It is currently self-funded by patients entirely or through research funding.

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention: (please copy the below questions and complete for each proposed item)

This application proposes the listing of a new MBS item for molecular testing in either patients with NSCLC (PICO set 1) or in patients with NSCLC for whom tissue-based testing is not an option or has failed (PICO set 2). For each of these PICO sets, two alternative MBS item descriptors are proposed. A reimbursement fee of $3,000.00 is proposed for all MBS item options.

This proposed fee has been determined following consultation with pathology labs that have experience providing the tissue-based and liquid biopsy-based NGS service in either a private or research capacity, and that include members of the RCPA. The 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. The cost breakdown of the proposed MBS item fee is provided in an attachment (Liquid biopsy cost breakdown for proposed MBS fee.xlsx).

The proposed fee is necessarily higher than the reimbursement currently offered for tissue-based testing. As highlighted by the RCPA in their statement of clinical relevance, the reimbursement for liquid biopsy would need to be significantly higher than tissue-based testing due to the higher sensitivity assays that are required that are costlier per test than tissue-based testing. Due to the low ctDNA fraction in cfDNA, a higher sequencing depth is required for a liquid biopsy to provide the sensitivity needed to accurately detect variants. There was strong consensus among the pathology laboratories regarding a potential reimbursement fee for liquid biopsy, which was in line with the RCPA's position, and the cost of homologous recombination deficiency (HRD) status testing, reimbursed at $3,000.00 (MBS item 73307), was considered a reasonable benchmark with respect to the level of sequencing and resources required.

Assay costs are incorporated into the library preparation and sequencing components of the cost breakdown, forming the largest portion of the total cost. The proposed fee 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.

Other variables in the practical and technical logistics of delivering a liquid biopsy service can factor into the cost of a liquid biopsy test per patient. All pathology labs consulted emphasised that a key consideration driving up the cost per patient with liquid biopsy over tissue-based NGS is economies of scale, where multiple samples (patients) must be run in a batch for the test to be cost-effective. Running fewer than the maximum allowed number of samples at a time becomes more costly as the same amount of resource and consumables are used. Nevertheless, this may be required in cases of clinical urgency, even as the listing of liquid biopsy on the MBS is anticipated to increase the number of requests for the service, thus the proposed item fee factors in the potential need for the assay to be run below maximum capacity.

Pathology overhead costs include the maintenance and service of instruments, data storage, quality assurance programmes, validation, rental and staffing.

With the above considerations, the estimated total cost per test according to the pathology labs surveyed for this application was in the range of $2,000.00 to $3,500.00, dependent upon on the panel size, sequencing depth and sample throughput. Based on the consensus of the feedback received and benchmarking against the HRD test, a total fee of $3,000 per patient is proposed as a reasonable fee for liquid biopsy. This would cover the necessary sequencing depth and the minimum genes listed in the MBS item description and ensure that minimal or no out-of-pocket costs to the patient.

Proposed item details – Option A

MBS item number (where used as a template for the proposed item)	MBS items 73445, 73446, 73447 and 73448 (haematological cancer panel tests) are used as a template for the proposed item descriptor
Category number	6
Category description	Pathology services – P7 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, METexon14sk, 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 details – Option B

MBS item number (where used as a template for the proposed item)	MBS items 73437, 73438 and 73439 (multi-gene panel tests of tumour tissue) are used as a template for the proposed item descriptor
Category number	6
Category description	Pathology services – P7 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 • to determine access to specific therapies relevant to these variants listed on the PBS; or • 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.

Algorithms

Preparation for using the health technology

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

Adult patients are diagnosed with NSCLC by pathological confirmation. Note that the proposed eligible population excludes patients with suspected lung cancer with no histological/pathological tissue confirmation of NSCLC. Following initial diagnosis, patients are referred by a specialist for tissue-based molecular testing to identify any actionable alterations. A tissue sample may be stored and available for analysis from the initial diagnosis, or a tissue rebiopsy may be warranted if tissue is insufficient following pathological diagnosis. As it is an invasive surgical procedure, patients might not be medically fit or a candidate for tissue rebiopsy and would be eligible for a liquid biopsy.

Additionally, patients who undergo tissue testing may have inconclusive results or test failure due to factors such as insufficient tissue or insufficient nucleic acid extraction, after which, the patient would be eligible for a liquid biopsy. This circumvents the need for a tissue rebiopsy for repeat testing.

Patients who progress are referred by a specialist for a tissue rebiopsy and tissue-based testing if feasible, otherwise the patient would be eligible for a liquid biopsy. In case of tissue test failure, the patient would also be eligible for liquid biopsy.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology? (please highlight your response)

Yes No

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

There is no anticipated change prior to the use of a liquid biopsy as patients will still require a tissue biopsy for the diagnosis of NSCLC or post-progression evaluation (where rebiopsy is feasible) prior to molecular biomarker testing.

Use of the health technology

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

Healthcare resources that are used in conjunction with liquid biopsy include peripheral venous blood collection.

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

N/A

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

Patients for whom tissue rebiopsy/testing is not an option would undergo venous blood sampling in place of no healthcare resource use.

Patients who fail tissue testing would undergo venous blood sampling in place of a rebiopsy.

Clinical management after the use of health technology

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

Pathology laboratories will utilise NGS-based gene panels to test for actionable alterations. Patients who receive a liquid biopsy and who test positive for actionable alterations will receive appropriate targeted therapy to manage their NSCLC. Patients with no actionable alterations will receive non-targeted therapy.

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

In the absence of testing, patients will receive non-targeted therapies to manage their NSCLC.

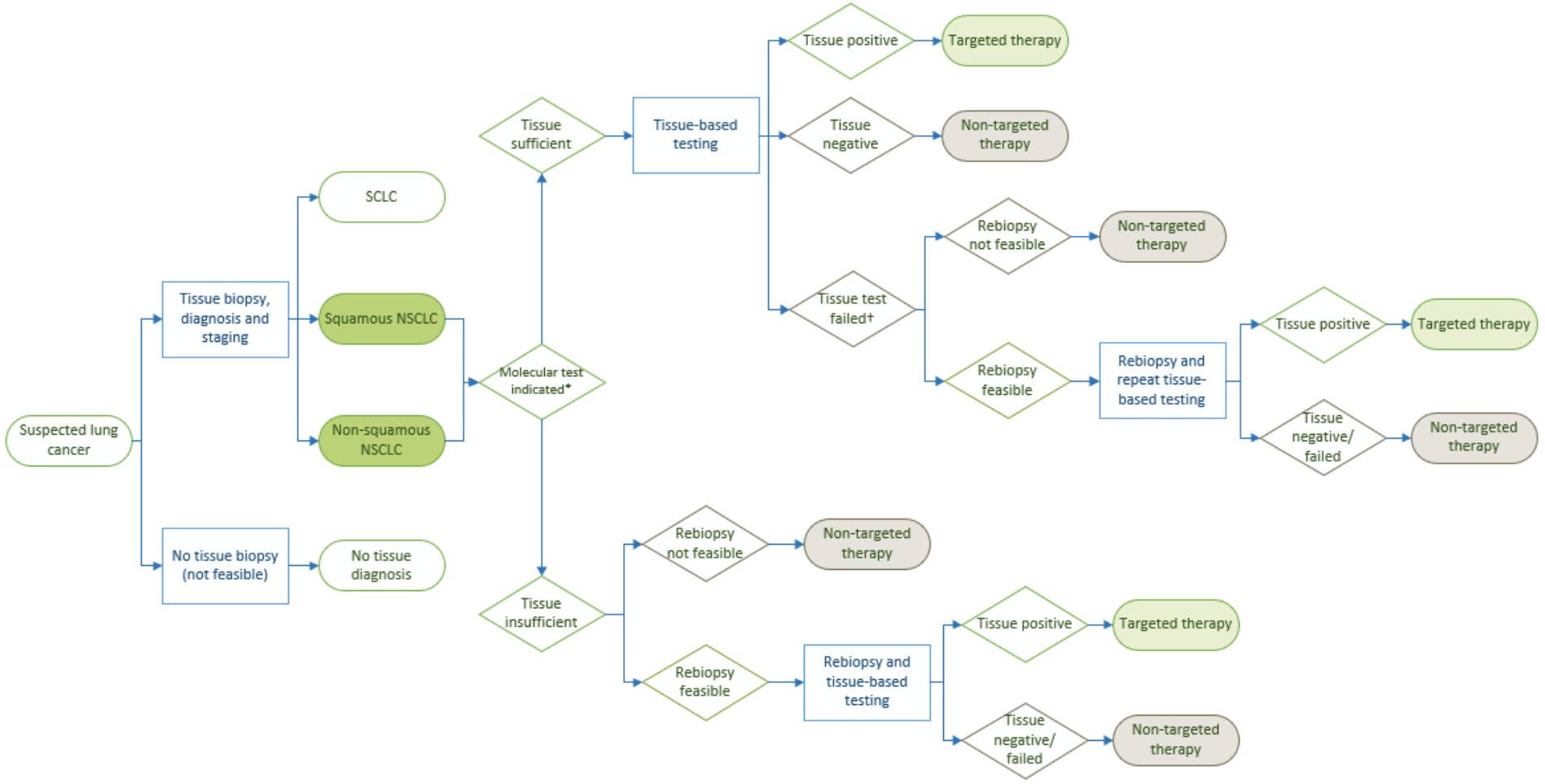
Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

The availability of liquid biopsy will enable the identification of a larger proportion of patients with actionable alterations. The additional patients identified would be eligible for targeted therapy to manage their NSCLC, who would not otherwise under current standard of care. The number of tissue rebiopsies is also expected to decrease with the use of liquid biopsy.

Algorithms

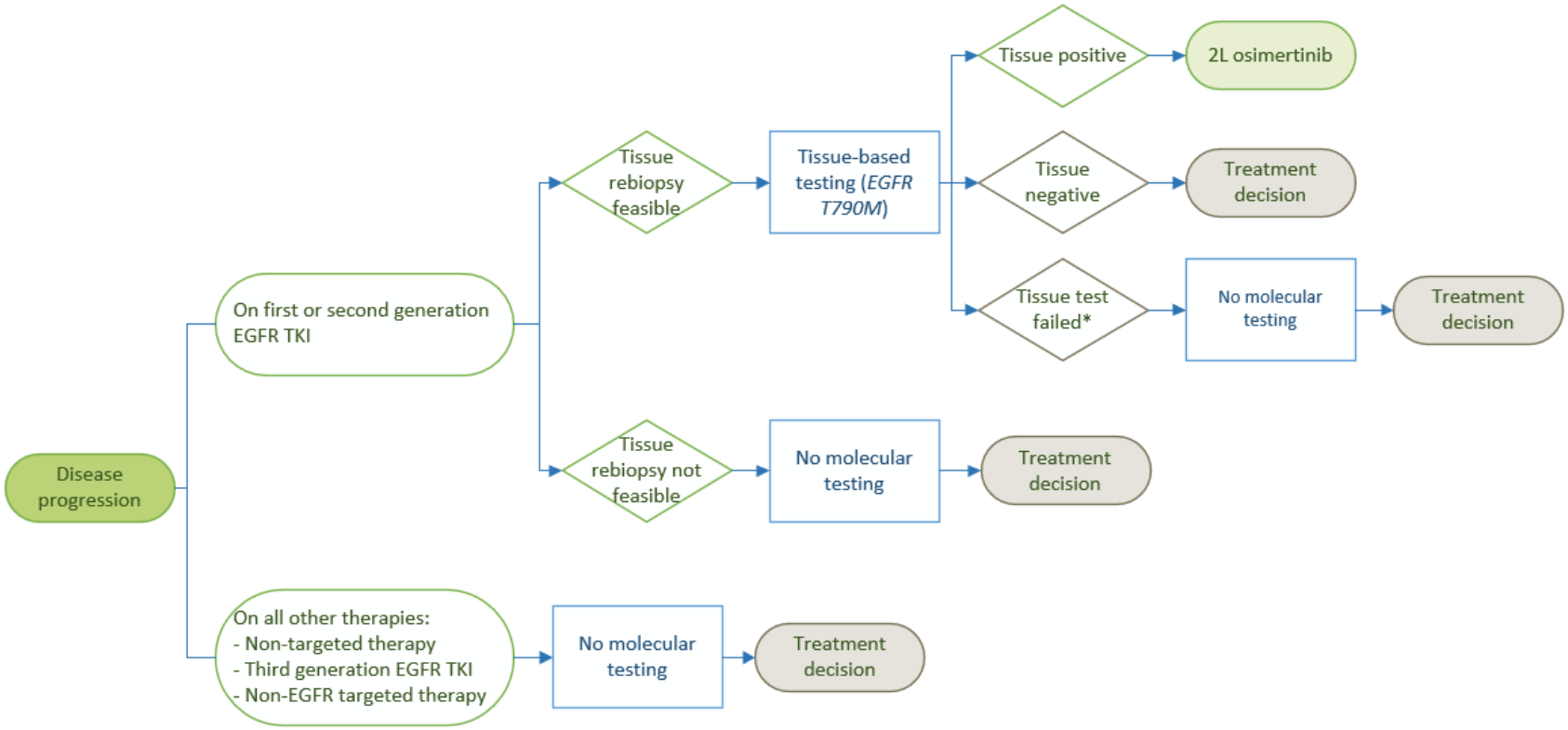
Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Figure 1 Current clinical management algorithm without liquid biopsy (new diagnosis)



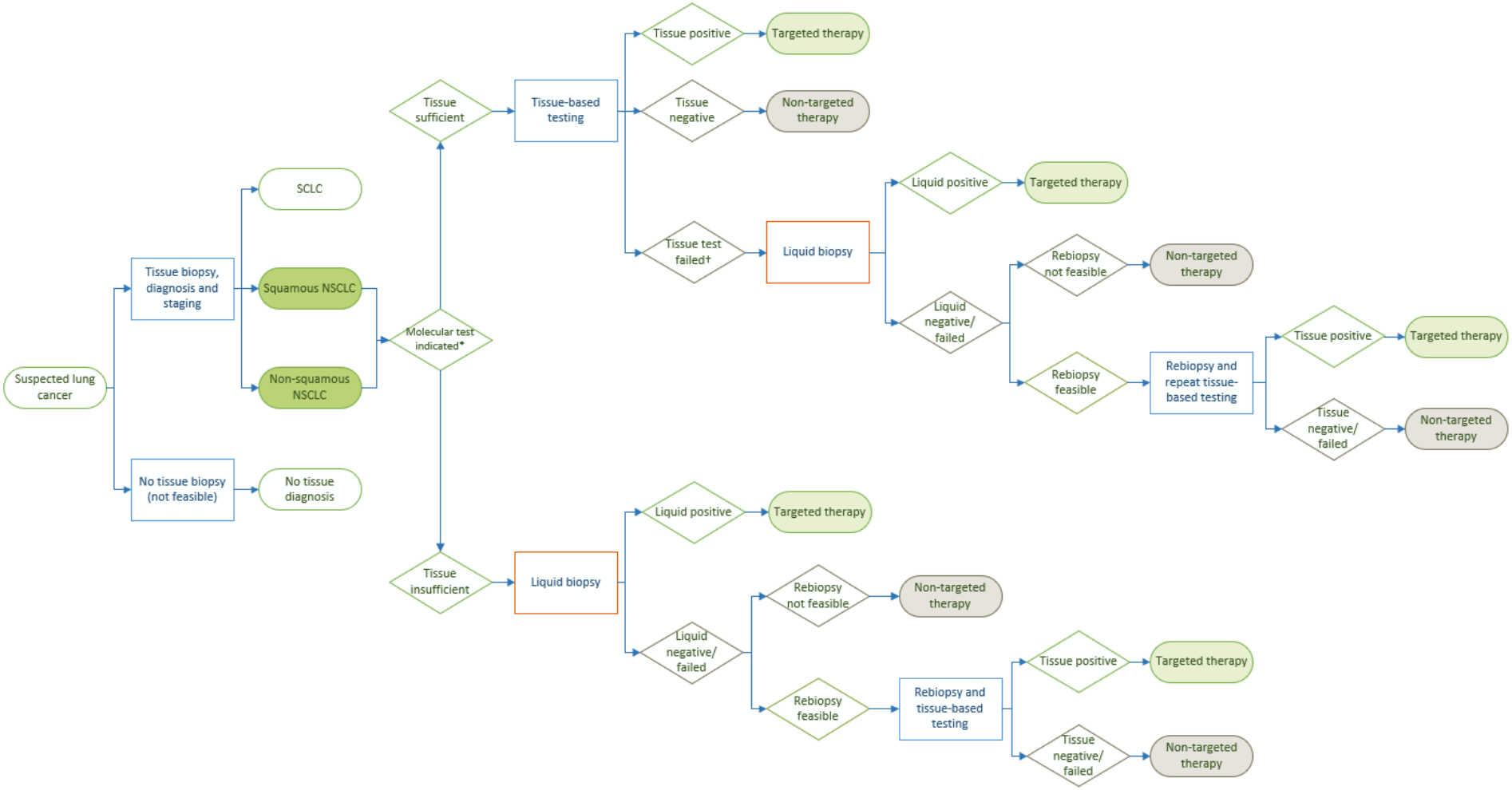
Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer
* Reflex molecular testing usually performed for non-squamous NSCLC; molecular testing performed upon request by the specialist for SCLC (considerations may include light or never smokers)
‡ Reasons for tissue test failure may include insufficient tissue, insufficient nucleic acid extracted or failure of NGS library preparation

Figure 2 Current clinical management algorithm without liquid biopsy (relapse)



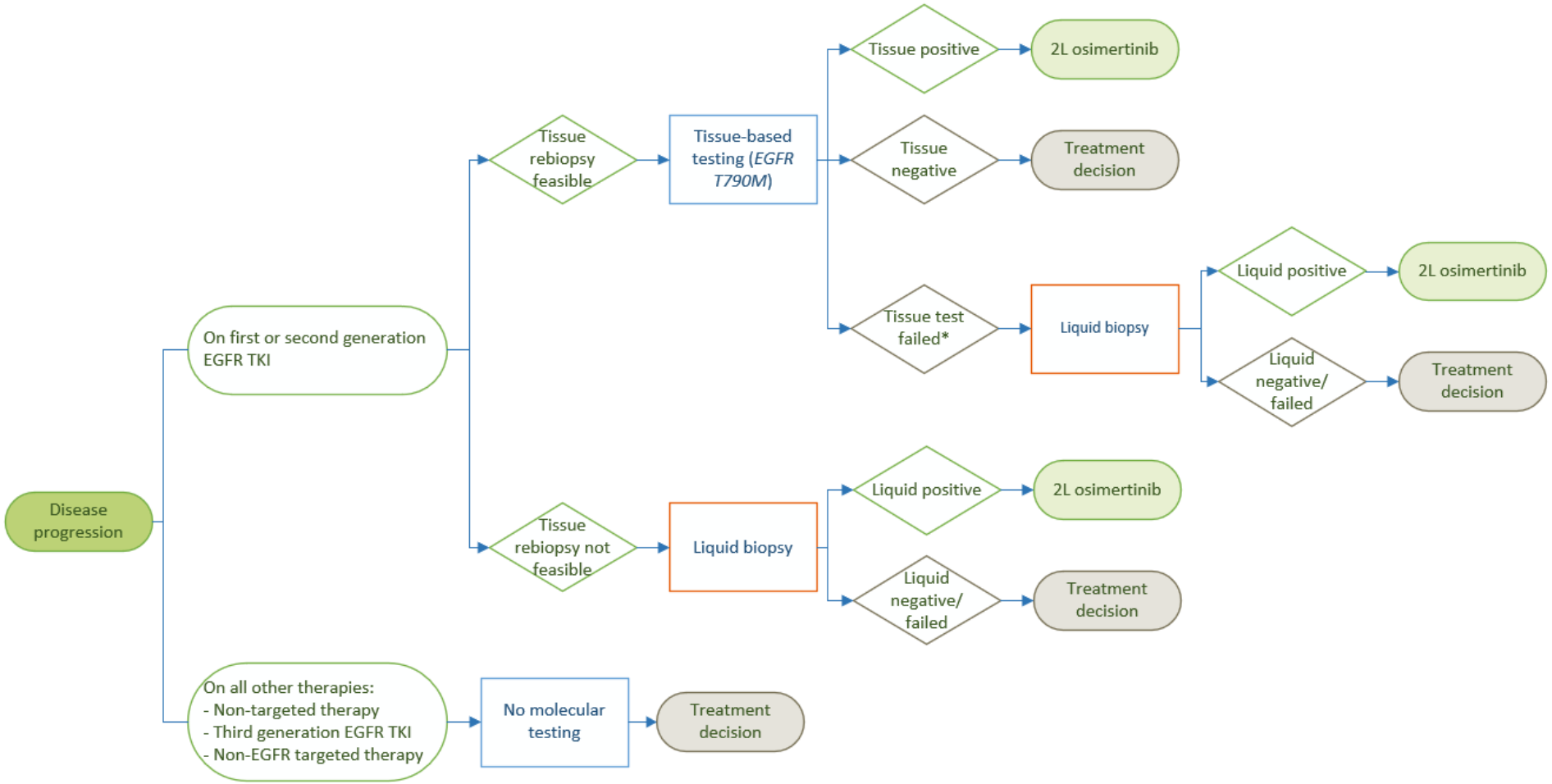
Abbreviations: 2L, second line; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor
* Reasons for tissue test failure may include insufficient tissue, insufficient nucleic acid extracted or failure of NGS library preparation

Figure 3 Proposed clinical management algorithm with liquid biopsy (new diagnosis)



Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer
* Reflex molecular testing usually performed for non-squamous NSCLC; molecular testing performed upon request by the specialist for SCLC (considerations may include light or never smokers)
‡ Reasons for tissue test failure may include insufficient tissue, insufficient nucleic acid extracted or failure of NGS library preparation

Figure 4 Proposed clinical management algorithm with liquid biopsy (relapse)



Abbreviations: 2L, second line; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor
* Reasons for tissue test failure may include insufficient tissue, insufficient nucleic acid extracted or failure of NGS library preparation

Claims

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

☒ Superior
☐ Non-inferior
☐ Inferior

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

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.

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

NSCLC has a poor prognosis with low 5-year survival rates. The advent of targeted therapies has greatly improved patient outcomes, but access to therapy and positive clinical outcomes are dependent on the identification of targetable genetic alterations via biomarker molecular testing in a timely manner. As such, patients currently unable to undergo tissue testing are not assessed for treatment eligibility, denying equitable access to treatment in this patient group. It has also been demonstrated that NSCLC patients with detectable ctDNA have a less favourable prognosis. It is crucial that patients are tested where possible to optimise treatment and improve patient outcomes, as undergenotyping not only results in missed treatment opportunities, but also inappropriate use of therapies likely to be ineffective (Leighl et al. 2019).

Identify how the proposed technology achieves the intended patient outcomes:

Access to liquid biopsy testing improves health outcomes for patients by providing access to targeted therapy, where relevant, with proven efficacy and safety. Patients with actionable alterations treated with targeted therapy have improved overall survival, progression-free survival and associated quality of life.

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

A change in clinical management?	Yes	No
A change in health outcome?	Yes	No
Other benefits?	Yes	No

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

N/A

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

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

Liquid biopsy is proposed as an additional test to current standard of care testing and therefore, is more costly than current standard of care.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology

	Type of study design	Identifier	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1	Clinical guidelines	Riely, 2024	NCCN Clinical Practice Guidelines in Oncology: Non-small cell lung cancer	Molecular testing via biopsy and/or plasma testing is recommended. Combinations of tissue and plasma testing, either concurrently or in sequence, are acceptable.	https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf https://pubmed.ncbi.nlm.nih.gov/38754467/	17/05/2024
2	Clinical guidelines	Lindeman, 2018	Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors	In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA assay to identify *EGFR* mutations. Cell-free DNA can be used to "rule in" targetable mutations when tissue is limited or hard to obtain	https://www.jmdjournal.org/article/S1525-1578(17)30590-1/fulltext (updated) https://pubmed.ncbi.nlm.nih.gov/23552377/ (original)	23/01/2018
3	Clinical guidelines	Hendriks, 2023	Oncogene-addicted metastatic non-small cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up	cfDNA can be used to test for oncogenic drivers and resistance mutations. Patients with a negative cfDNA blood test still require tissue biopsy. Genomic analysis by NGS (tissue, or cfDNA followed by tissue if no target is found with cfDNA) should be made available to a patient who develops resistance to EGFR-TKI	https://www.annalsofoncology.org/article/S0923-7534(22)04781-0/fulltext	24/01/2023

	Type of study design	Identifier	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
4	International prospective cohort study (yield; longitudinal accuracy)	Jee, 2022	Overall survival with circulating tumor DNA-guided therapy in advanced non-small cell lung cancer	(N=1,127) Among the 722 (64%) patients with detectable ctDNA, 255 (23%) matched to targeted therapy by ctDNA sequencing had longer survival than those not treated with targeted therapy (HR, 0.63; 95% CI, 0.52-0.76; P < 0.001). Genomic alterations in ctDNA not detected by time-matched tissue sequencing were found in 25% of the patients	https://pubmed.ncbi.nlm.nih.gov/36357680/	November 2022
5	Retrospective cohort study from one database (diagnostic accuracy; longitudinal accuracy)	Tran, 2021	Clinical outcomes in non-small-cell lung cancer patients treated with *EGFR*-tyrosine kinase inhibitors and other targeted therapies based on tumor versus plasma genomic profiling	(N=1971) In advanced NSCLC with either ctDNA or tissue NGS, there were no differences in progression-free survival with treatment based on tissue or ctDNA. Concordance between tests >97%, sensitivity of 91.7%, and specificity of 99.7%.	https://ascopubs.org/doi/10.1200/PO.20.00532	05/08/2021
6	Single-centre cohort study (treatment allocation; yield)	Aggarwal, 2019	Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer	N=220 Out of 94 patients who only received plasma NGS (tissue not ordered), 19 received targeted therapy (19/94=20%) Of 101 patients who only received plasma NGS results (79 tissue failed/ 22 biopsy not possible), 31 received targeted therapy (18 from failed tissue, 3 from biopsy not possible) (31/101=31%)	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6396811/	11/10/2018

	Type of study design	Identifier	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
7	Prospective single-centre cohort study (diagnostic accuracy)	Fernandes, 2021	Clinical Application of Next-Generation Sequencing of Plasma Cell-Free DNA for Genotyping Untreated Advanced Non-Small Cell Lung Cancer	N=115 NGS-based ctDNA revealed a diagnostic performance with 81.0% sensitivity, 95.3% specificity, 94.4% PPV, 83.6% NPV, test accuracy of 88.2%. Detection of ctDNA alterations was statistically associated with metastatic disease (p = 0.013)	https://pubmed.ncbi.nlm.nih.gov/34070940/	13/06/2021
8	Retrospective single-centre cohort study (change in management)	Bustamante Alvarez, 2021	Treatment of Non-Small-Cell Lung Cancer Based on Circulating Cell-Free DNA and Impact of Variation Allele Frequency	N= 143. A total of 94 patients had tissue and cfDNA testing within 12 weeks of each other, 49 patients had liquid biopsy only. A total of 8 patients started targeted therapy based on liquid biopsy results. In 5/8 patients experienced tissue failure (63%), 1/8 tissue was not ordered as LB results available early.	https://www.clinical-lung-cancer.com/article/S1525-7304(20)30340-5/abstract	1/12/2020
9	Retrospective single-centre cohort study (change in management)	Mack, 2020	Spectrum of Driver Mutations and Clinical Impact of Circulating Tumor DNA Analysis in Non–Small Cell Lung Cancer: Analysis of Over 8000 Cases	N=8388 patients received liquid biopsy between June 2014-October 2016. Of these, n=879 patients did not receive any tissue testing and 252/879 (29%) were positive for actionable genetic alterations. Half of these patients became eligible for targeted therapy.	https://pubmed.ncbi.nlm.nih.gov/32365229/	04/05/2020
10	Prospective single-centre study (change in management)	Sugimoto, 2023	A Large-Scale Prospective Concordance Study of Plasma- and Tissue-Based Next-Generation Targeted Sequencing for Advanced Non–Small Cell Lung Cancer (LC-SCRUM-Liquid	N=1,062 patients had paired tissue and blood sample for genomic profiling. A total of 46 patients received positive liquid results and tissue testing failure. 13 patients received targeted therapy based on liquid biopsy results alone.	https://aacrjournals.org/clincancerres/article/29/8/1506/725072/A-Large-Scale-Prospective-Concordance-Study-of	14/04/2023

	Type of study design	Identifier	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
11	Retrospective cohort study (diagnostic accuracy)	Schouten, 2021	Clinical Utility of Plasma-Based Comprehensive Molecular Profiling in Advanced Non–Small-Cell Lung Cancer	(N=209) Metastatic NSCLC patients with pre-treatment plasma samples compared to tissue. Concordance between SoC-TMP and plasma-CMP was 86.6% for potentially targetable drivers. Clinical sensitivity of plasma-CMP was 75.2% for any oncogenic driver. Specificity and positive predictive value were more than 90% for all oncogenic drivers	https://ascopubs.org/doi/10.1200/PO.20.00450	09/07/2021

Abbreviations: CAD, Canadian dollars; cfDNA, cell-free DNA; EGFR, epidermal growth factor receptor; EGFR-TKI, epidermal growth factor receptor – tyrosine kinase inhibitor ; HR, hazard ratio; ICER, incremental cost effectiveness ratio ; IV, intravenous; NGS, next-generation sequencing; NPV, negative predictive value; NSCLC, non-small cell lung cancer; PPV, positive predictive value; plasma-CMP, plasma- comprehensive molecular profiling; QALY, Quality adjusted life-year; SOC, standard of care; SOC-TMP, current standard-of-care protocolled tissue-based molecular profiling.

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