

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1798 – Liquid biopsy genetic testing in patients with non-small cell lung cancer

Applicant: AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo
Australia, Illumina, SOPHiA Genetics and Thermo Fisher
Scientific

Date of MSAC consideration: 27 November 2025

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of testing circulating tumour DNA (ctDNA) in plasma using next-generation sequencing (NGS) for the characterisation of clinically actionable genetic alterations in patients with non-small cell lung cancer (NSCLC) was received from the HTAnalysts on behalf of a cross-industry consortium consisting of AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo Australia, Illumina, SOPHiA Genetics and Thermo Fisher Scientific (hereafter defined as ‘the applicant’), by the Department of Health, Disability and Ageing.

MSAC noted that liquid biopsy is a new technique developed to detect tumours and their features by analysing biomarkers like circulating tumour cells, ctDNA, exosomes, extracellular vesicles, micro ribonucleic acid) in bodily fluid samples (e.g., blood, urine, saliva, cerebrospinal fluid, etc.).¹ MSAC noted that plasma-based ctDNA testing (using NGS) is the focus of the current application.

2. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of plasma based ctDNA testing to detect clinically actionable genetic alterations in patients with NSCLC.

MSAC considered that the application proposed a broader testing population than agreed by the PICO Advisory Subcommittee (PASC). MSAC noted that there was an unaddressed codependency for each of the 3 proposed populations, as the clinical utility of the proposed ctDNA-based genetic testing is to identify biomarkers in patients with NSCLC to access PBS-listed targeted therapies. However, MSAC considered that the application had not adequately considered the clinical utility of ctDNA-based genetic testing in any of the 3 proposed populations or the subsequent impact on costs and health outcomes from changes to patient management after the test.

Furthermore, the application did not consider the implication that discordant results (e.g., test positive from ctDNA but test negative from tumour tissue) might identify a population in whom

¹ Yin H, Zhang M, Zhang Y, Zhang X, Zhang X, Zhang B. Liquid biopsies in cancer. *Mol Biomed*. 2025 Mar 20;6(1):18. doi: 10.1186/s43556-025-00257-8. PMID: 40108089; PMCID: PMC11923355.

the clinical and cost-effectiveness of targeted therapies has not been assessed by the Pharmaceutical Benefits Advisory Committee (PBAC).

In addition to the issues of codependency and unclear clinical utility, MSAC considered that there was little clinical evidence to support the use of ctDNA-based genetic testing in population 1 (suspected NSCLC), a population that PASC recommended be excluded from further assessment, and part of population 2 (newly diagnosed NSCLC), those with early-stage disease. For population 3 (progressing NSCLC), MSAC considered that the clinical utility of ctDNA-based genetic testing is currently limited but might improve as new second-line targeted therapies become available that are based on second-line biomarker status (clinical trials in progress).

MSAC further noted that the PBAC Executive at its October 2025 meeting considered that the proposed use of ctDNA-based testing, if MBS-listed, could increase the number of NSCLC patients eligible for PBS-subsidised targeted therapies and therefore might have an impact on existing risk-share arrangements of targeted therapies. Given the interdependent nature of ctDNA-based testing and the provision of targeted therapies, both MSAC and the PBAC Executive therefore advised that any application for ctDNA testing, including this application, should be submitted as a PBAC/MSAC “codependent” application and should comprehensively address clinical effectiveness, cost-effectiveness and the potential budgetary impact for the Australian Government.

MSAC considered the introduction of ctDNA testing represents a significant shift from the current standard practice that uses tissue-based testing to identify tumour biomarkers. MSAC therefore advised that a framework be developed for assessing ctDNA-based testing to guide future assessment of ctDNA-testing.

Consumer summary

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. This application requested public subsidy on the Medicare Benefits Schedule (MBS) for a technology commonly called liquid biopsy for patients with confirmed or suspected NSCLC.

This application was submitted by HTAnalysts on behalf of the following companies: AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo Australia, Illumina, SOPHiA Genetics and Thermo Fisher Scientific.

To confirm a diagnosis of NSCLC, a patient has an operation in which a small sample of tissue is taken from the cancer, called a tumour biopsy. Some of the tissue collected in the biopsy is tested to determine the grade and stage for the cancer. There are different kinds of treatments for NSCLC. An individual patient may need to have multiple treatments or add or change to new treatments over time. For many treatments, genetic testing of tumour tissue is needed, to help make decisions about whether a particular treatment is a good choice for the individual patient. Patients found to have certain genetic changes may be eligible to access relevant targeted treatment on the Pharmaceutical Benefits Scheme (PBS).

In the proposed test, a patient has a blood test that can detect whether there are small pieces of genetic material from tumours circulating in the patient's blood stream, called 'circulating tumour DNA' (ctDNA). A method of genetic testing called next-generation sequencing is then used to read ctDNA, quickly and accurately, looking for specific changes, or variants that may help guide the selection of treatment.

The application requested public subsidy for ctDNA genetic testing in 3 patient groups. The first patient group (population 1) are patients who are suspected of having NSCLC but where this has not been confirmed. The second patient group (population 2) are patients with a confirmed diagnosis of NSCLC but who did not have enough tumour tissue sample left from their biopsy for genetic testing, or the sample failed testing. The third patient group (population 3) are patients with a confirmed diagnosis of NSCLC, whose cancer has progressed despite

Consumer summary

receiving a first line of treatment, and where there is not enough tissue sample left from their first biopsy to be able to run the genetic testing on it.

Using ctDNA, instead of tumour tissue, for genetic testing means that patients can have a blood test for genetic testing instead of tissue biopsy. This is particularly useful if there is no (or not enough) tumour tissue for genetic testing. However, genetic testing using ctDNA represents a big change from testing tumour tissue and may produce different results from genetic testing using tumour tissue sample. Some genetic variants of interest may not be found from a blood test sample. The evidence showed that ctDNA testing can miss genetic changes that would be found in tumour tissue testing. ctDNA testing also has the potential to identify genetic variants (for eligibility for treatment) for some patients who otherwise would have tested negative had tumour tissue testing been used. It is not known whether patients with genetic alterations in ctDNA will have the same response to targeted treatment as patients who have the genetic alteration in their tumour tissue.

MSAC noted that there was little evidence presented for population 1 (suspected NSCLC). MSAC agreed with the PICO Advisory Subcommittee (PASC) that population 1 should be excluded from further assessment.

MSAC noted that population 2 (newly diagnosed with NSCLC) has more evidence compared with populations 1 and 3. MSAC considered that since these patients (population 2) already have a confirmed diagnosis, they might be able to benefit from PBS-listed treatments. Using ctDNA testing could avoid patients needing to get repeat biopsy operations in cases where there was not enough tumour tissue left for genetic testing. However, MSAC considered that the introduction of ctDNA genetic testing would result in increased costs for both MBS and PBS and it is not known if the treatment will be as effective. MSAC considered that PBAC advice is required. MSAC also noted there was an unclear benefit for testing in early-stage disease.

For population 3 (progressing NSCLC), MSAC noted that currently none of the second-line targeted therapies available on the PBS in Australia require patients to have another genetic test. As a result, patients may undergo testing but the results, positive or negative, would not change the PBS-funded treatments available for them to access. MSAC considered this testing may be useful in the future if there are new medicines for NSCLC that need this type of testing.

Although MSAC recognised there may be some benefits to using ctDNA testing for some people in population 2 – including that it is faster and safer than a rebiopsy – it did not support listing the proposed services on the MBS. MSAC advised that ctDNA and tumour tissue testing identify different groups of patients for access to medicines on the PBS. The PBAC also needs to see an application comparing the therapy outcomes from tissue-based testing and ctDNA testing. As this new testing is to guide which medicines people can use on the PBS, MSAC considered that it should be resubmitted as a codependent application.

MSAC noted that using ctDNA-based testing would be a big change from current practice which relies on tissue samples to find the genetic variants that inform clinical decisions for relevant treatment. MSAC requested that a working group be established to develop a framework to assist future assessment of ctDNA testing.

MSAC's advice to the Commonwealth Minister for Health, Disability and Ageing

MSAC did not support public funding of ctDNA testing to detect genetic alterations to determine eligibility for relevant treatments on the PBS in patients with NSCLC. MSAC considered ctDNA and tumour tissue testing identify different patients as being eligible for targeted therapies on the PBS. It is not known if the targeted therapies work as well for patients who have genetic alterations on ctDNA only. For this reason, MSAC advised that the application should be re-submitted and considered jointly by the PBAC and MSAC.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted this was an application requesting MBS listing of ctDNA genetic testing using NGS to characterise clinically actionable genetic variants in patients with NSCLC. The application was submitted by HTAnalysts, on behalf of a cross-industry consortium comprising AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo Australia, Illumina, SOPHiA Genetics and Thermo Fisher Scientific.

MSAC recalled it had previously considered and supported tumour tissue testing for patients with a new diagnosis of NSCLC, for a range of actionable variants (that is, those with targeted treatments listed on the PBS). The most recent consideration in November 2022 resulted in the creation of MBS items [73437](#), [73438](#) and [73439](#) for multigene panel testing of tumour tissue to detect variants in several different genes to determine eligibility for a relevant treatment under the PBS. MSAC noted patients with locally advanced or metastatic NSCLC who have progressed while on, or after treatment with, an epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI) can access an additional test of tumour tissue to determine if the tumour has the resistant variant *EGFR* T790M ([MBS item 73351](#)).

MSAC noted that the public consultation input was supportive of the application.

The applicant was granted a hearing at the November 2025 MSAC meeting to support its proposal.

MSAC noted that the applicant-developed assessment report (ADAR) proposed 3 populations.

- Population 1 (suspected NSCLC): Patients with suspected NSCLC for whom tissue biopsy is not available.
- Population 2 (newly diagnosed NSCLC): Patients newly clinically diagnosed with lung cancer and histologically or cytologically confirmed NSCLC whose initial tissue biopsy was insufficient for tissue-based genetic testing or failed tissue-based genetic testing.
- Population 3 (progressing NSCLC): Patients with recurrence or progression of NSCLC disease on first-line treatment with targeted therapy, e.g. EGFR-TKIs.

MSAC considered that the ADAR proposed a broader testing population than agreed by PASC in April 2025. MSAC noted that despite PASC's advice that population 1 should be excluded from assessment (as PBS restrictions for NSCLC require a histologically or cytologically confirmed diagnosis of NSCLC), the ADAR had included population 1 for MSAC consideration.

For population 2, MSAC noted that PASC had advised adding 'unresectable or metastatic' to the population definition as it was most likely that surgical resection would not be feasible in patients at this disease stage and therefore tumour tissue would be more difficult to access. MSAC noted that the applicant agreed in its pre-Evaluation Subcommittee (ESC) response that restricting population 2 to unresectable or metastatic disease might be appropriate to prioritise patients with advanced disease as they have greater clinical need than those in early stage.

For population 2, MSAC also noted that the ADAR did not follow PASC's advice to use ctDNA testing only as a second-line test when tissue-based genetic testing fails or when the biopsy tissue was insufficient and rebiopsy is not possible. MSAC noted that the pre-MSAC response agreed with PASC advice but also reiterated that ctDNA testing should be a second-line test when tissue rebiopsy is feasible, with tissue rebiopsy and testing used third-line if the ctDNA test result returns negative. At the hearing, MSAC asked the applicant to clarify the proposed place of ctDNA testing in the clinical management algorithm, and if it was intended to be a replacement or an additional test to tumour tissue-based genetic testing. The applicant's clinical expert advised at the hearing that in many patients both ctDNA testing and tumour tissue testing would be performed, as ctDNA testing results can be returned more quickly but tumour tissue testing is

still required. The applicant's clinical expert also advised that all non-informative ctDNA test results would be followed with a tissue rebiopsy and tissue testing, whereas the ADAR base case assumed 80% of patients would proceed to rebiopsy following a negative ctDNA result. Therefore, MSAC considered that for population 2, the relative use of ctDNA testing, tumour tissue testing, and rebiopsy was uncertain. MSAC noted departmental advice that concurrent testing of tumour tissue and ctDNA is not eligible for MBS funding under the *Health Insurance Act 1973*, as the MBS will only fund the test that most accurately describes the service rendered in the same request episode.

MSAC noted that the ADAR did not nominate a specific assay or methodology but anticipated that both commercial in-vitro diagnostic (IVD) devices registered on the Australian Register of Therapeutic Goods (ARTG) and in-house IVDs would be utilised. MSAC noted the ADAR's list of laboratories in Australia that were accredited or seeking accreditation by NATA to provide ctDNA genetic testing services at the time. MSAC, however, noted variability in NGS capabilities and test platform differences across laboratories in Australia. MSAC noted that technical differences with NGS testing platforms affect quality assurance as accuracy may vary depending on whether hybrid capture or polymerase chain reaction (PCR) amplicon-based sequencing is used for target enrichment.

MSAC noted ctDNA testing may have reduced sensitivity for detecting copy number variations or gene fusions. MSAC noted in tissue-based and ctDNA-based testing, RNA-based assays are more sensitive and accurate than DNA sequencing in detecting fusions. Also, some variants, such as loss of heterozygosity and low-level copy number gains or losses, are more difficult to detect using ctDNA testing assays. In addition, MSAC noted as RNA is more labile in nature, specialised blood collection tubes, optimised transportation and thorough sample processing can help to preserve both cell-free (cf)DNA and cfRNA integrity for analysis. MSAC noted, at the hearing, the applicant's expert clarified that the proposed panel testing was ctDNA (not RNA) based.

MSAC noted that the applicant initially proposed an MBS fee of \$3,000 for ctDNA testing but later amended the proposed fee to \$2,200 to \$2,500 in the pre-MSAC response. MSAC noted that a comparable tumour tissue test on the MBS ([MBS item 73437](#)) which tests tumour tissue has a fee of \$1,247.00, while a commercial organisation in Australia charges \$1,320 for ctDNA NGS panel testing². MSAC therefore considered that the amended proposed fee of \$2,200-\$2,500 was too high. MSAC noted that work is underway by Genomics Australia to support MSAC to develop a standardised approach to fee-setting for genetic and genomic pathology items under MSAC consideration.

Regarding safety of the ctDNA testing procedure, MSAC noted it is non-inferior to no molecular testing, due to minor adverse events associated with venepuncture. MSAC concluded that ctDNA genetic testing has non-inferior safety compared to no molecular testing, but superior safety compared to a tissue rebiopsy.

MSAC noted that, currently, nearly all the medicines on the PBS targeting oncogenic drivers in NSCLC explicitly specify that the biomarker must be identified 'in tumour material'. The exceptions are larotrectinib and combined dabrafenib and trametinib therapy.³ MSAC noted in the pre-MSAC response, the applicant argued that ctDNA is tumour material, citing support from the Thoracic Oncology Group Australasia (TOGA). MSAC considered using ctDNA to determine eligibility for PBS-listed medicines needs to be considered by the PBAC, as relying on ctDNA could

² [Test-Request-Form v17.pdf](#) (accessed on 4 December 2025)

³ Larotrectinib for solid tumours (of any type) with confirmed *NTRK* gene fusion. The condition must be confirmed to be positive for a *NTRK* gene fusion prior to treatment initiation with this drug through a pathology report from an Approved Pathology Authority - provide the following evidence: (i) the date of the pathology report substantiating the positive *NTRK* gene fusion, (ii) the name of the pathology service provider. Dabrafenib for stage IV (metastatic) NSCLC. The condition must be positive for a *BRAF* V600E mutation.

identify a new population for PBS-listed treatments because results of ctDNA could be different from those from tissue testing.

MSAC noted the applicant in its pre-MSAC response argued that the current application, like MSAC application [1721](#), sought public funding of a new diagnostic technology linked to existing PBS-listed therapies and therefore the applicant disagreed with MSAC ESC that MSAC application [1782](#) was a relevant precedent for codependency. MSAC disagreed with the pre-MSAC response, because application 1721 was for an alternative testing approach of an NGS panel to simultaneously detect genetic variants on tumour tissue as a replacement for individual, sequential testing on tumour tissue using other testing methods. On the other hand, the current application proposed testing using a different type of sample and may yield discordant results. MSAC therefore considered a codependent submission is required because ctDNA testing would identify a new population for PBS-listed therapies that is different to the population identified by tumour testing.

MSAC noted that there was an unaddressed codependency for each of the 3 populations, as the clinical utility of the proposed ctDNA-based genetic testing is to identify biomarkers in patients with NSCLC to access PBS-listed targeted therapies, but the application had not adequately considered the clinical utility of ctDNA-based genetic testing in any of the 3 proposed populations or the subsequent impact on costs and health outcomes from changes in patient management after the test.

MSAC noted the clinical evidence base the ADAR presented for the 3 populations.

For population 1, MSAC noted there was very limited evidence for identifying clinically actionable variants in patients suspected of having NSCLC. Those without a clinically actionable variant are unlikely to benefit from the test. Further, MSAC noted other cancer types, such as pure squamous cell carcinomas, rarely have currently targetable oncogenic driver variants. MSAC considered that there is limited clinical utility for ctDNA testing without a diagnosis of NSCLC because identifying variants would not lead to changes in treatment as current PBS restrictions for targeted therapies require histological confirmation of NSCLC. MSAC noted that the pre-MSAC response agreed with MSAC ESC that the PBAC's advice is warranted for population 1.

For population 2, MSAC noted the overall concordance across 10 studies comparing ctDNA NGS testing to tissue NGS was comparable (Negative Percent Agreement [NPA/specificity]: 0.90; 95% CI: 0.86–0.93; Positive Percent Agreement [PPA/sensitivity]: 0.68; 95% CI: 0.62–0.75). ctDNA testing has a 98% to 100% test success rate, and a likely faster turnaround time (TAT) of about 6 to 21 days compared to tissue biopsy (success rate 60–88%), resulting in faster treatment initiation times. At the hearing, MSAC noted the applicant's clinical expert stated that with ctDNA results TAT typically ranges from 3-4 days whereas tissue testing generally requires an average of 3 weeks to obtain results. MSAC acknowledged that ctDNA testing was faster. However, MSAC did not accept that faster treatment initiation was linked to improved health outcomes in the proposed ctDNA positive populations as MSAC considered patients who are ctDNA biomarker positive but tumour biomarker negative may not respond as well to biomarker-targeted treatments. MSAC also noted that, for rural and remote locations, there could be delays in ctDNA testing as well, but that a blood test may be more accessible for people in these areas. MSAC noted pre-PASC consultation feedback from the Thoracic Society of Australia and New Zealand (TSANZ) that it would be appropriate to include a restriction to the proposed listing, if approved, to ensure patients have testing performed on the best available sample rather than the most convenient.

For population 2, MSAC noted that the ADAR did not present any direct evidence that compared ctDNA testing plus targeted treatment to no molecular testing plus standard treatment. MSAC noted that actionable variant detection rates for ctDNA testing ranged from 27.2% to 29.1%. Of

the 3 studies that examined cases of discordant results (ctDNA positive but tissue-negative), MSAC noted that treatment changes occurred in 43–75% in patients newly diagnosed with NSCLC. MSAC considered the ADAR's presented clinical evidence did not address whether patients whose ctDNA is biomarker positive, but who are biomarker negative on tumour testing, would respond as well to the biomarker-targeted treatments. MSAC considered this was important because there is discordance between ctDNA and tumour testing and the evidence for the targeted therapies has been based on biomarker status in tumour samples. Therefore, MSAC considered the magnitude of benefit of the targeted treatments in this population remains unknown.

MSAC noted that studies demonstrated changes in patient management for Population 2. One study emphasized the impact of turnaround time, with 73.5% of treatment decisions guided by plasma testing simply because results were available sooner. MSAC noted that data on rebiopsy avoided was limited: one case series reported that among patients with tissue testing failure due to tissue insufficiency, 86.7% avoided re-biopsy by undergoing ctDNA NGS testing, with only 13.3% requiring repeat procedures.

During the MSAC hearing, the applicant's clinical expert indicated that in clinical practice, all patients would eventually undergo conventional biopsy (if possible), although some procedures may be delayed due to availability of ctDNA results.

MSAC agreed with ESC that ctDNA testing shows the most clinical benefit for population 2 patients with unresectable or metastatic NSCLC, whilst noting that the codependency issues and consequences were unaddressed in the ADAR. MSAC considered clinical benefit for patients in population 2 with early-stage disease and/or prior tissue biopsy was limited, and similar codependency concerns and lack of data for superior health outcomes remain.

For population 3, MSAC noted that a published systematic review and meta-analysis (Nam 2021⁴) of 21 studies on tissue adequacy of percutaneous transthoracic needle biopsy (PTNB) for molecular analysis in patients with NSCLC reported an overall pooled tissue adequacy rate of 0.89, including initial biopsy and rebiopsy after therapy, with adequacy rate defined as the proportion of procedures that yielded an adequate amount of tumour tissue for molecular testing of at least one of *EGFR*, *ALK*, *ROS1*, *KRAS* or *RET*. MSAC, however, considered that the actual proportion of patients who would be considered unsuitable for tissue biopsy in Australia was uncertain. MSAC noted that the meta-analysis was restricted to PTNB and excluded studies of bronchoscopy or endobronchial ultrasound-guided (EBUS) procedure. MSAC noted that PTNB was only one of the diagnostic methods for obtaining tissue samples for molecular analysis and was usually for peripheral lesions whereas other methods (e.g., EBUS) might be amenable for population 3 with greater disease burden. In addition, MSAC considered the applicability of the results to Australia was uncertain as two-thirds of the included studies were conducted in Asia with higher rates of actionable mutations. MSAC also noted great heterogeneity among the studies.

MSAC noted for population 3, the 3 studies the ADAR presented reported concordance rates with considerable variability (PPA: 41.7%–68.4%; NPA: 16.7%–80.0%). Regarding yield, MSAC noted evidence suggested clinically actionable variants were identified in 33.3% of patients which is lower than those observed in Asian populations⁵. Therefore, MSAC noted, for population 3, ctDNA resulted in smaller yields of clinically actionable variants than testing of tumour tissue, and there

⁴ Nam BD, Yoon SH, Hong H, Hwang JH, Goo JM, Park S. Tissue Adequacy and Safety of Percutaneous Transthoracic Needle Biopsy for Molecular Analysis in Non-Small Cell Lung Cancer: A Systematic Review and Meta-analysis. *Korean J Radiol.* 2021 Dec;22(12):2082-2093. doi: 10.3348/kjr.2021.0244. Epub 2021 Aug 31. PMID: 34564960; PMCID: PMC8628152.

⁵ Sabari, JK, et al 2019, 'A Prospective Study of Circulating Tumor DNA to Guide Matched Targeted Therapy in Lung Cancers', *J Natl Cancer Inst*, vol. 111, no. 6, Jun 1, pp. 575-583 10.1093/jnci/djy156

was a trend towards poorer concordance between ctDNA results and tumour tissue results in patients tested post-progression than in treatment naive patients (population 2). However, MSAC noted if the comparator is no testing, testing with ctDNA would identify more patients with variants.

MSAC noted that a single study (Sabari 2019) provided evidence that post-progression testing may detect actionable variants broader than just *EGFR* T790M. However, MSAC also noted that all patients in the study were classified as having a partial response to their second-line targeted treatment. MSAC noted that the ADAR suggested that a partial response may be more likely than a complete response in patients with more advanced disease. MSAC considered the evidence was insufficient to claim that ctDNA testing is superior to no testing and use of non-targeted treatment in population 3, as there were no studies comparing second-line targeted therapy versus standard of care treatments for those without actionable variants after failure of first-line targeted treatments. MSAC noted that no clinical claim was made regarding the comparator that PASC suggested, namely rebiopsy and testing of tumour tissue. MSAC considered the limited comparative evidence suggested that ctDNA testing is inferior to testing of tumour tissue if the number of variants tested were the same for each technique because it detects fewer clinically actionable variants than tumour testing.

MSAC noted a key issue for all 3 proposed populations was the potential of discordant results between ctDNA and tissue biopsy testing. MSAC noted one study by Oxnard et al. (2016)⁶ found that tissue heterogeneity was associated with most of the tissue-plasma discordance, suggesting some discordance was not due to false positives. MSAC further noted it is possible that low ctDNA levels can also prevent detection of the variant (a false negative case). MSAC considered that discordance could also be due to test platforms or substrates, and concluded that the reasons for and clinical consequences of discordance were uncertain. Further MSAC noted the potential of ctDNA testing to detect variants that are unrelated to the tumour (such as clonal haematopoiesis of indeterminate potential [CHIP]) remains. MSAC noted the applicant's clinical expert at the hearing considered that discordant results are rare in their experience and that they considered ctDNA to have high sensitivity for detecting clinically actionable variants. The applicant's clinical expert also claimed that clinicians would be confident in recommending a therapy based on ctDNA test results alone.

MSAC also noted that at the time of its consideration, for population 3, there were no PBS-listed second-line therapies that require testing after first-line treatment. MSAC noted that there was only one second-line PBS-listed targeted therapy (osimertinib) which can also be used as first-line therapy. MSAC noted in clinical practice osimertinib is the preferred treatment option for first-line therapy in patients with an eligible *EGFR* variant. At the hearing, the applicant stated that additional therapies are in development, and even though there are no relevant medicines currently listed on the PBS, there is value in knowing a patient's ctDNA test results. MSAC considered that if there are no relevant PBS-listed therapies, then the value of knowing about a specific genetic variant was limited. MSAC acknowledged that while such information could facilitate access to clinical trials, MBS items cannot be used for this purpose.

MSAC noted that the ADAR presented a separate cost-effectiveness analysis for each of the 3 proposed populations, with the incremental cost-effectiveness ratio (ICER) expressed as the incremental cost per additional actionable alteration identified, MSAC noted that PASC had suggested a cost-utility analysis would be most appropriate given the claimed impacts of testing on changes in treatment and improved health outcomes. MSAC agreed with ESC that the approach in the ADAR essentially truncated the economic evaluation at the time of treatment

⁶ Oxnard, Geoffrey R., et al. Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2016 Oct 1;34(28):3375-82.

decision-making without capturing the downstream changes in costs and effectiveness that would be expected to accrue from changes in management. MSAC noted that the ADAR and the pre-MSAC response argued that modelling of these downstream consequences was not necessary because the PBAC had already established the cost-effectiveness of the PBS-listed medicines that patients would be accessing as a consequence of ctDNA testing. MSAC considered this approach was not appropriate because it assumes each PBS-listed medicine is equally effective in the new population who are biomarker positive on ctDNA but may not be biomarker positive on tumour tissue. MSAC advised that these downstream changes must be supported by evidence and included in the economic evaluation. MSAC considered that the cost-effectiveness of each treatment in the population identified by ctDNA testing needs to be considered by the PBAC, along with changes in financial impacts to the PBS arising from increased numbers of eligible patients, and implications for any existing relevant risk-share or price agreements.

MSAC noted that the pre-MSAC response highlighted the complexity in modelling the downstream treatment changes and claimed this would require reliance on outdated clinical data that do not reflect current standards of care. MSAC acknowledged that this might be challenging for the applicant, since it would need to assess ICERs and financial projections for medicines not manufactured by the sponsors. However, MSAC considered that without this additional modelling, the economic evaluation is not sufficient for decision-making. MSAC considered this emphasised why a codependent application is necessary, so that all inputs and costs could be considered appropriately for both the MBS and PBS.

MSAC noted that the ADAR's estimated net cost to the MBS was \$9.5 million in Year 1 of listing, rising to \$18.8 million in Year 6. MSAC noted the commentary considered that the ADAR might have underestimated the financial impact for population 1 but overestimated for populations 2 and 3. MSAC noted that the commentary's revised estimates on net cost to the MBS was \$5.4 million in Year 1, rising to \$10.8 million in Year 6.

MSAC noted the ADAR reported that ctDNA testing for identifying genetic variants in NSCLC was increasingly being used in international jurisdictions, with varying levels of uptake and subsidy. For example, ctDNA testing is now included in the National genomic test directory for cancer which specifies the genomic tests commissioned by the National Health Service in England (NHSE),⁷ following a successful NHSE-commissioned ctDNA pilot study.⁸ MSAC noted that pilot data (unpublished) in lung cancer showed that some patients received the results of ctDNA testing needed to make treatment decisions 16 days earlier than the standard cancer tissue biopsy approach.⁹ However, MSAC considered that any system-level process improvement observed in the UK pilot study may not be as relevant/applicable in the Australia context given our access to care at baseline (e.g., shorter times to see a specialist in Australia and the time between a ctDNA result and a tissue biopsy result).

MSAC considered the introduction of ctDNA testing represents a significant shift from the current standard practice that uses tissue-based testing to identify actionable tumour biomarkers.

MSAC considered that broad-ranging codependency issues exist for most of the patients for whom MBS listing is sought. When referred, the MSAC Executive at its October 2025 meeting

⁷ Multi-target ctDNA combined with multi-target NGS panel, in patients with radiologically suspected stage III/IV lung cancer, likely unsuitable for curative intent surgery or radical radiotherapy; and in patients with a confirmed new histological diagnosis of NSCLC, previously untreated for advanced disease where diagnostic molecular testing has failed, and an alternative option would be re-biopsy (source: Test code M4.14, National genomic test directory for cancer, Version 13.1, published 10 July 2025, NHS England; available: <https://www.england.nhs.uk/publication/national-genomic-test-directories/>).

⁸ <https://norththamesgenomics.nhs.uk/our-work/our-successes/ctdna/>

⁹ <https://www.england.nhs.uk/2025/05/nhs-first-in-world-to-roll-out-revolutionary-blood-test-for-cancer-patients/>

agreed with MSAC ESC that advice from the PBAC was required regarding the codependency. MSAC noted the PBAC Executive considered that the proposed use of ctDNA testing, if MBS-listed, could increase the number of NSCLC patients eligible for PBS-subsidised targeted therapies and therefore might have an impact on existing risk-share arrangements of targeted therapies.

Overall, MSAC did not support public funding of ctDNA testing to detect clinically actionable genetic alterations in any of the 3 proposed populations.

MSAC agreed with the PBAC Executive that, given the interdependent nature of ctDNA testing and the provision of targeted therapies, any application for ctDNA testing should be submitted as PBAC/MSAC codependent application and should comprehensively address clinical effectiveness, cost-effectiveness, and the potential budgetary impact for the Government.

MSAC considered there is limited clinical utility for testing in population 1 as they would not be eligible for PBS-funded therapies due to the absence of a confirmed diagnosis of NSCLC.

For population 2, MSAC advised that a re-application (as a codependent submission) should address the following:

- The population should be limited to the population confirmed by PASC - patients newly clinically diagnosed with unresectable or metastatic lung cancer and histologically or cytologically confirmed NSCLC whose initial tissue biopsy was insufficient for tissue-based genetic testing or failed tissue-based genetic testing.
- Clearly quantify the clinical utility of ctDNA testing arising from changes in management.
- Document inter-test variability, since some assays only test for known variants, while broader panels may miss rare or unexpected changes.
- Review the proposed fee for ctDNA genetic testing, which should be lowered, or better justified.
- Clarify the place of ctDNA testing in the proposed clinical management algorithm, specifically its use as a replacement test and in addition to tissue-based testing.
- Provide a full cost-utility analysis where possible that includes time to treat and linked quality of life (QoL) benefit in Australian practice, biopsies avoided, and an analysis that also meets the requirements of the PBAC.
- Revised utilisation and financial estimates that align with this population.

For population 3, MSAC considered that ctDNA testing may have a place in the future as these patients have progressed and may not be able to obtain/undergo a tumour tissue rebiopsy. MSAC considered that population 3 should be reconsidered when new second-line therapies become available (and require re-testing to determine eligibility) or, when more ctDNA evidence is gathered through ongoing clinical trials like the ASPIRATION-2 Liquid clinical trial.¹⁰

MSAC requested a working group be established to develop a framework to inform future assessments of ctDNA.

¹⁰ The ASPIRATION-2 Liquid study is an observation cohort study that plans to recruit 500 Australian adults with oncogene-driven metastatic NSCLC whose disease has progressed after first-line TKI therapy. At baseline, patients undergo testing and may receive ctDNA testing before starting prescribed second-line treatment. At first progression, patients undergo repeat testing including ctDNA testing, with subsequent cycles of treatment and testing continuing. The study receives funding from the Medical Research Future Fund (MRFF) Frontier Grant, an initiative of the Australian Government [<https://thoraciconcology.org.au/news/treatments/aspiration-2l-liquid-biopsy-clinical-trial-for-advanced-lung-cancer-patients-across-australia/>].

4. Background

MSAC has not previously considered ctDNA testing for the characterisation of actionable variants in NSCLC.

MSAC has previously considered tumour tissue testing for patients with a new diagnosis of NSCLC, for a range of actionable variants (those with targeted treatments listed on the Pharmaceutical Benefits Scheme (PBS), most recently supporting the introduction of 3 MBS items (MBS items 73437, 73438 and 73439) for multi-gene panel testing of tumour tissue to detect variants in at least epidermal growth factor receptor (*EGFR*), B-Raf proto-oncogene, serine/threonine kinase (*BRAF*), KRAS proto-oncogene, GTPase (*KRAS*), MET proto-oncogene, receptor tyrosine kinase (*MET*) exon 14 and/or fusion status of ALK receptor tyrosine kinase (*ALK*), ROS proto-oncogene 1 (*ROS1*), ret proto-oncogene (*RET*), neurotrophic receptor tyrosine kinase 1, 2 and 3 (*NTRK1*, *NTRK2* and *NTRK3*). In patients with locally advanced or metastatic NSCLC who have progressed while on or after treatment with an EGFR tyrosine kinase inhibitor (TKI) there is also an additional test of tumour tissue to determine if the tumour has the resistant variant *EGFR* T790M (MBS 73351).

Some of MSACs considerations of MSAC 1721 DCAR (Small gene panel testing NSCLC testing tumour tissue) are relevant to the current assessment. These have been summarised in Table 1.

Table 1 Summary of key matters of concern from MSAC 1721 PSD that may be relevant to MSAC 1798

Component	Matter of concern in MSAC 1721	How the current assessment report addresses similar issue
PBS listing	MSAC noted that current PBS listings for <i>ROS1</i> and <i>ALK</i> require detection to occur by FISH, and that amendments would need to be referred by the department to the Pharmaceutical Benefits Advisory Committee (PBAC) <i>MSAC 1721 PSD p3</i>	The current PBS listings for targeting variants in <i>EGFR</i> , <i>ALK</i> , <i>ROS1</i> , <i>METex14</i> and proposed listings for <i>RET</i> gene fusions would require amending as they currently specify “in tumour material” (and therefore referring by the department to PBAC). PBS listings for <i>NTRK</i> and proposed listing for <i>BRAF</i> V600E variant are silent on sample type.
Intervention (population 3)	MSAC foreshadowed that MBS item 73351 may eventually be altered to include NGS for other actionable resistance variants, including T790M, with currently reimbursed or future TKIs, or future antibody-drug conjugates. <i>MSAC 1721 PSD p4</i>	The ADAR proposed that the test used on or after progression while on a targeted treatment includes other actionable variants.
Clinical effectiveness	MSAC considered that an outstanding issue was the lack of documented improved outcomes with testing. <i>MSAC 1721 PSD p7</i>	A small volume of test to health outcomes was included.
Economics	MSAC noted that the economic evaluation was a cost-effectiveness analysis, where the primary outcome was a net change in patients determined to be eligible for targeted therapy. <i>MSAC 1721 PSD p8</i> MSAC supported the listing of the proposed MBS items because the evidence for NGS demonstrated its superior effectiveness owing to its improved test success rate (i.e., more samples with sufficient quantity and/or quality to be able to be successfully tested for variants), improved variant detection rate and superior safety due to the reduced need for rebiopsy compared with sequential single gene tests with acceptable cost effectiveness and financial implications. <i>MSAC 1721 PSD p8-9</i>	Current ADAR used a similar approach, using the primary outcome of net change in patients determined to be eligible for targeted therapy.

ADAR = Applicant Developed Assessment Report; *ALK* = ALK receptor tyrosine kinase; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; *EGFR* = epidermal growth factor receptor; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; NGS = next-generation sequencing; *NTRK* = neurotrophic receptor tyrosine kinase; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; *RET* = ret proto-oncogene; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase; T790M = Thr790Met, methionine for threonine at amino acid position 790; TKI = tyrosine kinase inhibitor.

Source: developed during the commentary by the assessment group

5. Prerequisites to implementation of any funding advice

In vitro diagnostics (IVDs) intended for use as a companion diagnostic for corresponding medicines or biological products are required to be assessed by the TGA. Commercial companion diagnostic IVDs on the Australian Register of Therapeutic Goods (ARTG) for NSCLC are shown in Table 2. In-house IVD companion diagnostics are required to be accredited by National Association of Testing Authorities (NATA), and meet the National Pathology Accreditation Advisory Council (NPAAC) standard. The NATA assessed, TGA-notified in-house IVD will need to be confirmed as available in NATA accredited laboratories in Australia.

Only one commercial multi-gene panel is currently registered as a companion diagnostic IVD with the TGA (Oncomine™Dx Target Test).

Table 2 IVD companion diagnostics listed on the ARTG

IVD companion diagnostic name	IVD-ARTG number	Biomarker
Droplex EGFR Mutation Test v2	430070	EGFR
Oncomine™Dx Target Test	426895	ALK, BRAF, EGFR L858R exon 19, EGFR exon 20, RET, ROS1
PD-L1 IHC 22C3 pharmDx	385791	PD-L1
PD-L1 IHC 22C3 pharmDx (Dako Omnis) /GE006	397615	PD-L1
Therascreen KRS RGQ PCR Kit	386490	KRAS
VENTANA anti-ALK (D5F3) Rabbit Monoclonal Primary Antibody	406279	ALK
VENTANA PD-L1 (SP263) Assay	401407	PD-L1

ALK = ALK receptor tyrosine kinase; ARTG = Australian Register of Therapeutic Goods; BRAF = B-Raf proto-oncogene, serine/threonine kinase; EGFR = epidermal growth factor receptor; IHC = immunohistochemistry; IVD = in vitro diagnostic; KRAS = KRAS proto-oncogene, GTPase; PD-L1 = Programmed Death-Ligand 1; RET = ret proto-oncogene; ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase
Source: <https://www.tga.gov.au/products/medical-devices/specific-types-medical-devices/companion-diagnostics-cdx-list>

Currently, PBS restrictions for nearly all the drugs targeting oncogenic drivers in NSCLC (i.e. osimertinib, erlotinib, gefinitib, afatinib, crizotinib, alectinib, brigatinib, ceritinib, lorlatinib, entrectinib, and tepotinib) specify that the biomarker must be identified “in tumour material”. The exceptions are larotrectinib and the proposed restriction for combined dabrafenib and trametinib, that are silent on the sample type in which the biomarker should be found. Advice would be needed from the PBAC regarding whether ctDNA constitutes tumour material for the purpose of determining eligibility for the PBS medicines listed above.

Furthermore, the PBS restrictions for NSCLC require a diagnosis of NSCLC which currently requires histological confirmation. The applicant proposed updating eligibility criteria for affected PBS medications to allow patients with suspected NSCLC and the relevant biomarker to be eligible for targeted treatments.

6. Proposal for public funding

The applicant developed assessment report (ADAR) proposed that there should be three new MBS items for ctDNA genetic testing in the following indications:

1. Patients with suspected NSCLC for whom tissue biopsy is not available (population 1, or ‘suspected NSCLC’).
2. Patients newly clinically diagnosed with lung cancer and histologically or cytologically confirmed NSCLC whose initial tissue biopsy was insufficient for tissue-based genetic testing or failed tissue-based genetic testing (population 2, or ‘newly diagnosed NSCLC’).
3. Patients with recurrence or progression of NSCLC disease on first-line treatment with targeted therapy where a post-progression tissue biopsy is not feasible or a post-progression tissue biopsy has failed (population 3, or ‘progressing NSCLC’).

For each population, the applicant provided two different options of MBS item descriptors.

For each indication, Option 1 omitted the purpose of testing and did not make it clear that the items cannot be co-claimed with MBS items for testing of tumour tissue. This would potentially allow testing for other purposes, such as determining prognosis (or determining the cause of

treatment-resistance), rather than being solely for the purpose of determining eligibility for targeted treatment as claimed in the ADAR. The commentary suggested that the proposed MBS items using option 1 should be deleted (AAAA, CCCC and EEEE). For each indication, Option 2 specified the purpose of the testing (“to determine eligibility for relevant treatments under the PBS”) and included appropriate restrictions to avoiding co-claiming with existing MBS items.

The commentary noted items proposed in the ADAR did not correspond to the wording supported by the PASC of the MSAC (the PASC-ratified proposed MBS items are also provided below). The PASC-ratified wording is more similar to existing MBS items for testing for biomarkers in patients with NSCLC, with extra specificity regarding the type of gene alteration required to be tested (e.g. fusion status should be sought for *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK2* and *NTRK3*). Furthermore, PASC suggested that the erb-b2 receptor tyrosine kinase 2 (*ERBB2*) (previously known as *HER2*) gene should not be included in the MBS item, as there is currently no PBS-listed targeted treatment for NSCLC requiring variants in this gene. While acknowledging that *ERBB2* may become relevant in the near future due to trastuzumab deruxtecan that targets HER2-positive cancer, PASC considered that the description of testing “at least” the listed genes would future-proof the descriptor.

The applicant preferred the language “to detect variants to include, but not be restricted to” rather than “to detect variants in at least” the relevant genes. The ADAR claimed that this would allow more flexibility in which multi-gene panels would be able to be used under the MBS items, and claimed that the minimal inclusion of the listed genes should not be a funding requirement. The commentary expressed concern as not all ctDNA NGS assays used in Australia would have the capability to detect both actionable variants and gene fusions, whether at the DNA or RNA level. However, the commentary considered that there is a risk that the proposed items could be used for a small multi-gene panel, that does not cover all the relevant actionable variants and gene fusions, with lower clinical utility than larger multi-gene panels. Furthermore, current MBS items including 73437, 73438 and 73439 utilise ‘at least’ in the item descriptor. This phrasing provides flexibility by enabling testing of additional clinically relevant genes within the single multi-gene panel beyond what has been considered in previous MSAC considerations.

Population 1

The three options of MBS item descriptor wording for population 1 (suspected NSCLC) are shown in

Table 3 to Table 5. The wording proposed by PASC is more specific in that the patient must be suspected of having NSCLC, rather than the test being available for all patients with lung cancer. The commentary noted if the item is open to all patients with lung cancer, it could result in the item being used to test those diagnosed with small cell lung cancer, for which the evidence had not been assessed.

Table 3 Applicant proposed item descriptor for ctDNA testing in patients suspected of having NSCLC (population 1), wording option 1

Category 6 – Pathology services – P7 Genetics
<p>MBS item AAAA</p> <p>Characterisation of a variant or variants in a multi-gene panel using circulating tumour nucleic acid from a plasma sample, requested by, or on behalf of, a specialist or consultant physician, to inform the clinical management of a patient with lung cancer, in whom tissue testing is not an option or has failed.</p> <p>Testing to include, but not be restricted to, <i>EGFR, BRAF, KRAS, MET_{Exon14sk}, ERBB2 (HER2), ALK, ROS1, RET, NTRK1, NTRK2</i> and <i>NTRK3</i>.</p>
Fee: \$3,000.00 Benefit: 75% = \$2,250.00 85% = \$2,897.60*

* Reflects the 1 November 2024 Greatest Permissible Gap (GPG) of \$102.40. All out-of-hospital Medicare services which have an MBS fee of \$683.00 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
 Source: Table 17, p 68 of MSAC 1798 ADAR

Table 4 Applicant proposed item descriptor for ctDNA testing in patients suspected of having NSCLC (population 1), wording option 2

Category 6 – Pathology services – P7 Genetics
<p>MBS item BBBB</p> <p>A circulating tumour nucleic acid-based multi-gene panel test of a plasma sample from a patient with lung cancer, in whom tissue testing is not an option or has failed, requested by, or on behalf of, a specialist or consultant physician:</p> <ul style="list-style-type: none"> a) to detect variants that include, but are not limited to, <i>EGFR, BRAF, KRAS, MET_{Exon14sk}, ERBB2 (HER2), ALK, ROS1, RET, NTRK1, NTRK2</i> and <i>NTRK3</i>; and b) to determine eligibility for relevant treatments under the Pharmaceutical Benefits Scheme (PBS); and c) not associated with a service to which item 73437, 73438, 72439, 73337, 73341, 73344, 73436 or 73351 applies.
Fee: \$3,000.00 Benefit: 75% = \$2,250.00 85% = \$2,897.60*

* Reflects the 1 November 2024 Greatest Permissible Gap of \$102.40. All out-of-hospital Medicare services which have an MBS fee of \$683.00 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
 Source: Table 18, p 69 of MSAC 1798 ADAR

Table 5 Proposed item descriptor for ctDNA testing in patients suspected of having NSCLC (population 1), wording option 3 (suggested by PASC)

Category 6 – Pathology services – P7 Genetics
<p>MBS item XXXX</p> <p>Characterisation of a variant or variants in a multi-gene panel using a circulating tumour, nucleic acid-based test on a plasma sample, from a patient with suspected NSCLC for whom tissue biopsy is not available, as requested by, or on behalf of, a specialist or consultant physician, if the test is:</p> <ul style="list-style-type: none"> a) to detect variants in at least, <i>EGFR, BRAF, KRAS, and MET_{Exon14}</i>, to determine eligibility for relevant treatments under the Pharmaceutical Benefits Scheme (PBS); and b) to detect fusion status of at least <i>ALK, ROS1, RET, NTRK1, NTRK2</i> and <i>NTRK3</i>; to determine eligibility for relevant treatments under the Pharmaceutical Benefits Scheme (PBS); and c) not associated with a service to which item 73437, 73438, 72439, 73337, 73341, 73344, 73436 or 73351 applies.
Fee: to be determined

Source: Table 9, p34, of MSAC 1798 Ratified PICO Confirmation

Population 2

The three wording options for an MBS item descriptor for population 2 (newly diagnosed NSCLC) are shown in Table 6 to Table 8. PASC had suggested that population 2 should be defined as patients diagnosed with NSCLC where a tissue rebiopsy is not feasible or where a tissue rebiopsy has failed. None of the proposed MBS items restrict their use to those unable to have a rebiopsy, or where a rebiopsy has failed (i.e. they allow use of ctDNA testing after the initial tissue biopsy has been insufficient or testing has failed, rather than requiring a rebiopsy if deemed feasible).

PASC advised that in newly diagnosed patients with NSCLC, that ctDNA testing be restricted to those with “unresectable or metastatic” disease, as it is likely that surgical resection would not be feasible in patients at this disease stage and tumour tissue would be more difficult to access. The applicant suggested that restricting the item would be inconsistent with the use of new-generation targeted therapies in early-stage disease. The commentary noted it was unclear what proportion of patients with early-stage disease would have surgical resection but insufficient tumour tissue for informative tissue-based genetic testing.

Table 6 Applicant proposed item descriptor for ctDNA testing in patients with newly diagnosed NSCLC (population 2), wording option 1

Category 6 – Pathology services – P7 Genetics
<p>MBS item CCCC</p> <p>Characterisation of a variant or variants in a multi-gene panel using circulating tumour nucleic acid from a plasma sample, requested by, or on behalf of, a specialist or consultant physician, to inform the clinical management of a patient with NSCLC, in whom tissue testing is not an option or has failed.</p> <p>Testing to include, but not be restricted to, <i>EGFR, BRAF, KRAS, MET_{exon14sk}, ERBB2 (HER2), ALK, ROS1, RET, NTRK1, NTRK2</i> and <i>NTRK3</i>.</p>
Fee: \$3,000.00 Benefit: 75% = \$2,250.00 85% = \$2,897.60*

* Reflects the 1 November 2024 Greatest Permissible Gap of \$102.40. All out-of-hospital Medicare services which have an MBS fee of \$683.00 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
Source: Table 19, p 69 of MSAC 1798 ADAR

Table 7 Applicant proposed item descriptor for ctDNA testing in patients with newly diagnosed NSCLC (population 2), wording option 2

Category 6 – Pathology services – P7 Genetics
<p>MBS item DDDD</p> <p>A circulating tumour nucleic acid-based multi-gene panel test of a plasma sample from 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:</p> <ul style="list-style-type: none"> a) to detect variants that include, but are not restricted to, <i>EGFR, BRAF, KRAS, MET_{exon14sk}, ERBB2 (HER2), ALK, ROS1, RET, NTRK1, NTRK2</i> and <i>NTRK3</i>; and b) to determine eligibility for relevant treatments under the Pharmaceutical Benefits Scheme (PBS); and c) not associated with a service to which item 73437, 73438, 72439, 73337, 73341, 73344, 73436 or 73351 applies.
Fee: \$3,000.00 Benefit: 75% = \$2,250.00 85% = \$2,897.60*

* Reflects the 1 November 2024 Greatest Permissible Gap of \$102.40. All out-of-hospital Medicare services which have an MBS fee of \$683.00 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
Source: Table 20, p 70 of MSAC 1798 ADAR

Table 8 Proposed item descriptor for ctDNA testing in patients with newly diagnosed NSCLC (population 2), wording option 3 (suggested by PASC)

Category 6 – Pathology services – P7 Genetics
<p>MBS item YYYY</p> <p>Characterisation of a variant or variants in a multi-gene panel using a circulating tumour, nucleic acid-based test on a plasma sample, from a patient with newly diagnosed unresectable or metastatic non-small cell lung cancer whose initial tissue biopsy is insufficient for tissue-based genetic testing or failed tissue-based genetic testing, for whom further tissue testing is not an option, as requested by, or on behalf of, a specialist or consultant physician, if the test is:</p> <ol style="list-style-type: none"> to detect variants in at least, <i>EGFR</i>, <i>BRAF</i>, <i>KRAS</i>, and <i>MET</i><i>Exon14</i>, to determine eligibility for relevant treatments under the Pharmaceutical Benefits Scheme (PBS); and to detect fusion status of at least <i>ALK</i>, <i>ROS1</i>, <i>RET</i>, <i>NTRK1</i>, <i>NTRK2</i> and <i>NTRK3</i>; to determine eligibility for relevant treatments under the Pharmaceutical Benefits Scheme (PBS); and not associated with a service to which item 73437, 73438, 72439, 73337, 73341, 73344, 73436 or 73351 applies.
Fee: to be determined

Source: Table 10, p35, of MSAC 1798 Ratified PICO Confirmation

Population 3

The three wording options for an MBS item descriptor for population 3 (those who have progressed on or after first-line targeted treatment for NSCLC) are shown in Table 9 to Table 11. The commentary noted none of the proposed wording versions restrict the use of the MBS items to those patients where a rebiopsy is infeasible, or where a rebiopsy and tissue-based genetic testing has failed (i.e. the item is broader than the proposed population). If MSAC decides that multi-gene panel testing for actionable variants post-recurrence/progression on targeted therapies for NSCLC has clinical utility and is cost-effective, then it may wish to consider whether modifications to current existing MBS items or creation of a new MBS item (or multiple items to allow for separate testing of DNA, RNA or both) should be considered to enable tissue-based testing for this purpose.

All of the proposed items were silent on the line of targeted treatment received. While the evidence was all in patients who had progressed after first-line targeted treatment, PASC noted that further progression of the disease on second- or later-line treatment is possible, and that a frequency limit to the test should apply¹¹.

Table 9 Applicant proposed item descriptor for ctDNA testing in patients with progressing NSCLC (population 3), wording option 1

Category 6 – Pathology services – P7 Genetics
<p>MBS item EEEE</p> <p>Characterisation of a variant or variants in a multi-gene panel using circulating tumour nucleic acid from a plasma sample, requested by, or on behalf of, a specialist or consultant physician, to inform the clinical management of a patient with NSCLC who is on targeted therapy and has evidence of progressed disease.</p> <p>Testing to include, but not be restricted to, <i>EGFR</i>, <i>BRAF</i>, <i>KRAS</i>, <i>MET</i><i>Exon14sk</i>, <i>ERBB2</i> (<i>HER2</i>), <i>ALK</i>, <i>ROS1</i>, <i>RET</i>, <i>NTRK1</i>, <i>NTRK2</i> and <i>NTRK3</i>.</p>
Fee: \$3,000.00 Benefit: 75% = \$2,250.00 85% = \$2,897.60*

* Reflects the 1 November 2024 Greatest Permissible Gap of \$102.40. All out-of-hospital Medicare services which have an MBS fee of \$683.00 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

Source: Table 21, p 70 of MSAC 1798 ADAR

¹¹ MSAC 1798 Ratified PICO Confirmation

Table 10 Applicant proposed item descriptor for ctDNA testing in patients with progressing NSCLC (population 3), wording option 2

Category 6 – Pathology services – P7 Genetics
<p>MBS item FFFF</p> <p>A circulating tumour nucleic acid-based multi-gene panel test of a plasma sample from a patient with NSCLC who is on targeted therapy and has evidence of progressed disease, requested by, or on behalf of, a specialist or consultant physician:</p> <ul style="list-style-type: none"> a) to detect variants that include, but are not limited to, <i>EGFR</i>, <i>BRAF</i>, <i>KRAS</i>, <i>MET</i>_{exon14sk}, <i>ERBB2</i> (<i>HER2</i>), <i>ALK</i>, <i>ROS1</i>, <i>RET</i>, <i>NTRK1</i>, <i>NTRK2</i> and <i>NTRK3</i>; and b) to determine eligibility for relevant treatments under the Pharmaceutical Benefits Scheme (PBS); and c) not associated with a service to which item 73437, 73438, 72439, 73337, 73341, 73344, 73436 or 73351 applies.
Fee: \$3,000.00 Benefit: 75% = \$2,250.00 85% = \$2,897.60*

* Reflects the 1 November 2024 Greatest Permissible Gap of \$102.40. All out-of-hospital Medicare services which have an MBS fee of \$683.00 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
Source: Table 22, p 70 of MSAC 1798 ADAR

Table 11 Proposed item descriptor for ctDNA testing in patients with progressing NSCLC (population 3), wording option 3 (proposed by PASC)

Category 6 – Pathology services – P7 Genetics
<p>MBS item ZZZZ</p> <p>Characterisation of a variant or variants in a multi-gene panel using a circulating tumour, nucleic acid-based test on a plasma sample, from a patient with non-small cell lung cancer who is on targeted therapy and has evidence of progressed disease, as requested by, or on behalf of, a specialist or consultant physician, if the test is:</p> <ul style="list-style-type: none"> a) to detect variants in at least, <i>EGFR</i>, <i>BRAF</i>, <i>KRAS</i>, and <i>MET</i>_{exon14}, to determine eligibility for relevant treatments under the Pharmaceutical Benefits Scheme (PBS); and b) to detect fusion status of at least <i>ALK</i>, <i>ROS1</i>, <i>RET</i>, <i>NTRK1</i>, <i>NTRK2</i> and <i>NTRK3</i>; to determine eligibility for relevant treatments under the Pharmaceutical Benefits Scheme (PBS); and c) not associated with a service to which item 73437, 73438, 72439, 73337, 73341, 73344, 73436 or 73351 applies.
Fee: to be determined

Source: Table 11, p35 of MSAC 1798 Ratified PICO Confirmation

Proposed fee

The applicant proposed MBS fee for each of the three indications was \$3,000, which was justified on the basis of the costs of specialised collection tubes and nucleic acid extraction (\$50), library preparation (\$700), sequencing (\$1,200), bioinformatics analysis (\$100), pathologist interpretation and reporting (\$100) and pathology laboratory overheads (\$800). The pathology overheads included the maintenance and service of instruments, data storage, quality assurance programs, validation, rental and staffing. The applicant further justified the fee by benchmarking to MBS item 73307 for testing of tumour tissue for homologous recombination deficiency status testing (with a fee of \$3,000).

The commentary noted an equivalent test on tumour tissue (MBS 73437) for detecting variants in at least *EGFR*, *BRAF*, *KRAS* and *MET*_{ex14} and fusion status in at least *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK2* and *NTRK3* has a fee of \$1,247.00, and if only DNA (MBS 73438) or RNA (MBS 73439) is tested (not both) then the fee is \$682.35. The commentary considered the proposal by the applicant to have a single high fee regardless of what is tested is inconsistent with the existing approach for testing of tumour tissue listed on the MBS.

7. Population

Lung cancer is the fifth most common cancer in Australia, and the most common cause of cancer-related deaths¹². There are two different histological types of lung cancer, the most common of which (85-90%) is NSCLC. The condition is most often diagnosed when already at an advanced stage of disease. Over 65% of cases of NSCLC have genomic alterations such as in the *EGFR*, *ALK*, *ROS1* genes, that can be targeted by treatments¹³. Testing for these oncogenic drivers is therefore part of standard practice, and currently requires a biopsy of tumour tissue, which is MBS-funded. However, not every patient has a tumour that is feasible to biopsy, due to factors such as location of tumour, or the retrieved tissue being insufficient to allow genetic testing (or results in an uninformative test result). In current practice, therefore, there are patients who are unable to receive PBS-listed targeted treatment for their NSCLC, due to the inability to undertake genetic testing. The applicant claims that the use of ctDNA genetic testing (NGS testing of circulating tumour DNA in plasma extracted from a blood sample) would address this unmet clinical need.

In the ADAR three populations were proposed to be eligible for ctDNA genetic testing:

- those suspected of having NSCLC (such as those with lung cancer identified on imaging), who could not have a biopsy to confirm that the tumour was NSCLC (population 1);
- those newly diagnosed with NSCLC who cannot tolerate a biopsy, or whose initial biopsy tissue was insufficient for tissue-based genetic testing or failed genetic testing (population 2); and
- those with NSCLC who had recurrence or progression of NSCLC on or after first-line treatment with targeted therapy, and could not tolerate a rebiopsy, or whose rebiopsy had failed to retrieve sufficient tissue for informative genetic testing (population 3).

In population 1, if a patient is suspected of having NSCLC and has a clinically actionable variant identified, there is a high likelihood that they have NSCLC, but this does not mean they would be eligible to receive PBS-subsidised treatment for NSCLC without histological or cytological confirmation. PASC recommended the exclusion of population 1, citing concerns related to i) the diagnostic uncertainty in this population due to the lack of a histological or cytological diagnosis of NSCLC, ii) a lack of clinical evidence and iii) complex interactions with current PBS eligibility, policy and clinical care. The commentary noted the ADAR still included this population, with the applicant emphasising that these concerns illustrate the high clinical need in a population that would otherwise have no options to allow access to targeted treatment.

PASC advised restricting population 2 to those patients diagnosed with NSCLC where a tissue rebiopsy is not feasible or where a tissue rebiopsy has failed. The ADAR amended this population to include those where the initial biopsy was insufficient for tissue-based genetic testing or failed tissue-based genetic testing. PASC had also suggested restricting population 2 to those whose cancer was unresectable or metastatic, which the applicant argued would not future-proof the item to allow for targeted treatments in early-stage disease. However, the commentary noted nearly all the included evidence for population 2 was in advanced NSCLC (locally advanced or metastatic). Early-stage disease is less likely to have circulating tumour DNA detected in the bloodstream¹⁴. The commentary noted there was therefore a biological rationale for less accurate results from ctDNA testing in early-stage disease than in advanced disease.

¹² <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/rankings>

¹³ Tan, A & Tan, D 2022, 'Targeted therapies for lung cancer patients with oncogenic driver molecular alterations', *J Clin Oncol*, vol. 40, no. 6, pp. 611-625

¹⁴ Connal, S, et al 2023, 'Liquid biopsies: the future of cancer early detection', *J Transl Med*, vol. 21, no. 1, Feb 11, p. 118 10.1186/s12967-023-03960-8.

Most PBS restrictions for targeted treatments for NSCLC are silent on the line of therapy they may be used for, meaning that if another actionable variant is identified post-relapse/progression, then the patient may receive another line of targeted treatment¹⁵. PASC advised the preferable option would be that patients should first have a rebiopsy attempted for tissue-based testing to identify further genetic alterations (prior to being eligible for a ctDNA testing, unless a rebiopsy is not feasible), but noted the only MBS-listed test for this purpose is restricted to testing of *EGFR-T790m* variant known to confer resistance.

In all three populations, the use of ctDNA testing is proposed as an alternative or replacement to no molecular testing (where a biopsy is not feasible), and for population 2, it may also be an alternative or replacement for rebiopsy and tissue-based genetic testing. The commentary noted the downstream implication of more patients being able to have genetic testing, is an increase in the number of patients potentially eligible for targeted treatment for NSCLC, which is claimed to result in superior health outcomes compared to non-targeted treatments that are available for NSCLC.

8. Comparator

Population 1: For patients suspected of having NSCLC, who do not have tumour tissue available or accessible for histological or cytological confirmation of NSCLC, the comparator was no molecular testing.

Population 2: For patients with newly diagnosed NSCLC, standard practice is to have tissue-based NGS panel testing at diagnosis. In those with insufficient tumour tissue from the initial biopsy, or where the tissue-based testing failed, the comparator options are either no molecular testing or to have a rebiopsy for tissue-based testing, where feasible.

Population 3: For patients who progressed after a first-generation *EGFR*-TKI (erlotinib, gefitinib, or afatinib) standard practice would be to undergo a rebiopsy and testing of tumour tissue for the resistant variant *EGFR T790M* under MBS item 73351, for the purposes of determining eligibility for second-line treatment with the third-generation *EGFR*-TKI osimertinib. When osimertinib was first introduced, it was restricted to being a second-line treatment, for use in those with the T790M variant. However, osimertinib has since become the preferred first-line treatment for those with advanced or metastatic NSCLC and an activating *EGFR* variant known to confer sensitivity to *EGFR* TKIs and has been PBS-listed for this indication. PBS-subsidised treatment with osimertinib is restricted to a single line of therapy, so those who have first-line osimertinib are not eligible to receive it in the second-line. This has resulted in the use of T790M testing under MBS 73351 greatly reducing. As such, the applicant proposed the comparator for population 3 (those who have progressed while on or after any targeted treatment for NSCLC) to be no molecular testing.

However, PASC suggested that the comparator for population 3 should include tissue-based testing post-progression, where it is feasible.

¹⁵ Note, if patients have received previous PBS-subsidised treatment targeting a particular variant (e.g. an *EGFR* TKI), they would be ineligible to receive a second *EGFR*-TKI for the same variant, unless they had developed intolerance to the first treatment necessitating a treatment withdrawal.

9. Summary of public consultation input

Consultation input was welcomed from:

1798 - ctDNA testing genetic testing in patients with non-small cell lung cancer	No. of Inputs Received
Organisations (11)	
I am providing input on behalf of a consumer group or organisation. Consumer organisations are not-for-profit organisations representing the interests of healthcare consumers, their families and carers.	4
I am providing input on behalf of a medical, health, or other (non-consumer) organisation. For example, input on behalf of a group of clinicians, research organisation, professional college, or from an organisation that produces a similar service or technology.	8
Health Professionals (1)	
I am a health professional or health academic working in the area.	1
Consumers (2)	
I have the health condition that this health service or technology is for.	1
I have the health condition that this health service or technology is for and have experience with the proposed health service or technology.	1
Grand Total	15

The organisations that submitted input were:

- Lung Foundation Australia (2)
- Thoracic Oncology Group of Australasia
- Medical Oncology Group of Australia
- The Thoracic Society of Australia and New Zealand
- Australian Genomics
- Human Genetics Society of Australasia Ltd
- Roche Diagnostics Australia
- InGeNA Limited
- Rare Cancers Australia
- ALK Positive Australia Inc
- Royal College of Pathologists of Australasia

Level of support for public funding

- Unanimous support for public funding of ctDNA testing.

Comments on PICO

- **Population:** Broad agreement; suggestions to include:
 - Patients with no actionable tissue findings.
 - Those clinically unsuitable for biopsy but suspected of NSCLC.
 - RCPA agreed with PASC that population 1 (suspected NSCLC) should be excluded from the application due to risk of misuse. RCPA reported that ctDNA testing would still be useful when NGS on the biopsy is suboptimal but still reportable, because suboptimal result may still include a definite driver mutation but potentially may miss other relevant subclonal variants in low coverage regions.
 - ALK Positive was concerned that population 3 was too narrow and advocated the broadening of population 3 from patients who progress on first-line targeted therapy

to patients who progress while on or after targeted therapy (any line), citing that it is an equity and patient outcome necessity.

- **Comparator:** Agreed upon.
 - ALK Positive expressed a strong belief that the evaluation should be against real-world comparators, i.e., tissue rebiopsy and tissue genotyping when feasible, ctDNA testing as the first choice when tissue is unsafe or infeasible, and ctDNA plus tissue testing in parallel when timeliness or risk warrant it.
- **Item Descriptor:**
 - Support for flexibility in genes tested.
 - Preference for brand-agnostic wording to improve access.
 - Mixed views on restrictions (e.g., TOGA supports best sample use; MOGA suggests one-time use).
 - RCPA agreed with the changes to the item descriptor for Population 2 marked up in red font in the PICO Confirmation. The original stipulation of 'not an option' was vague and could be misconstrued. RCPA recommended limiting the MBS item descriptors to 'non-squamous NSCLC' rather than all NSCLC, as the proposed test is not relevant for squamous NSCLC and could lead to overuse of the item.
 - ALK Positive advocated that the funded item must specify that ctDNA assays detect RNA in addition to DNA to ensure the alterations are relevant to patients, not just a narrow set of variants.
- **Fee:**
 - Generally agreed as appropriate.
 - Should consider sequencing depth and lab capacity.
 - RCPA supported the proposed fee of \$3,000 and cost breakdown provided in the PICO Confirmation. RCPA reported that *NTRK1/2/3* fusions are rare in NSCLC (<1%) and are difficult to detect on DNA sequencing due to the variability in the intronic breakpoints. This means large intronic regions need to be sequenced and for ctDNA sensitivity (to identify only a few reads supporting the variant) high depth requirements use up large amounts of sequencing, contributing to the proposed fee and limiting the number of samples on a flow cell.

Perceived Advantages

- Enables access to targeted therapies for patients unable to undergo tissue rebiopsy (e.g., due to tumour location, poor performance status or comorbidities, at high risk of medical complications like pneumothorax).
- Negate the need for second biopsy in cases of insufficient tissue testing.
- Faster turnaround times compared to tissue biopsy and better detection of tumour heterogeneity.
- Prevents hospitalisation from biopsy-related complications.
- Useful for patients with co-morbidities or in under-resourced hospitals; avoiding the need for a repeat biopsy especially for patients in rural/remote areas and reducing inequity.
- May detect actionable genetic alterations missed in tissue samples.
- Reduces financial, physical, and emotional burden for patients with lung cancer and their carers.

Perceived Disadvantages

- Variability in NGS capabilities across laboratories in Australia.

Support for Implementation and Issues

- High setup costs for equipment and staff training may hinder national implementation.

- RCPA reported that ctDNA testing does not need to be pathologist determinable as a new specimen (blood sample) is required, so a new request form from the treating doctor is needed.
- ALK Positive considered that laboratories must meet accreditation standards, with assays include safeguards such as filtering out clonal haematopoiesis and negative ctDNA testing reflexed to tissue when feasible. ALK Positive also advocates funding to include cerebrospinal fluid (csf)-based ctDNA testing in patients with brain-only progression.

10. Characteristics of the evidence base

Population 1

Only one study examined ctDNA testing in suspected NSCLC cases lacking pathological diagnosis, with reasons including advanced age (27.6%), cultural considerations (26.7%), previous biopsy failures (19.8%), technical challenges such as small or diffuse nodules or intolerance to biopsy (16.4%), and poor physical condition (9.5%). Five additional studies were included in the ADAR that assessed the use of ctDNA testing in those suspected of having NSCLC, who proceeded to have a pathological diagnosis (with/without tissue-based testing for molecular variants). An independent search found no additional studies relevant to the population with suspected NSCLC. The key features of these six studies are outlined in Table 12.

Table 12 Key features of the included evidence for patients suspected of having NSCLC (population 1)

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Performance of the test (concordance, yield)	Within-patient comparisons without a reference standard	☒ k=5 n=419	Moderate In order to have comparative results against tissue, the population had to include those where biopsy was feasible.
Change in patient management	Prospective case series, reporting on treatments received based on ctDNA testing results (no data on what treatments patients would have received in absence of ctDNA testing)	☒ k=3 n=249	Low to moderate Unclear what treatments would have received in the absence of pathological diagnosis.
Health outcomes	Naïve indirect comparison between treatment outcomes in those variant positive based on ctDNA testing vs tumour tissue	☒ k=1 n=391	High risk of bias due to confounding between studies (prognostic differences)

k = number of studies; n = number of patients; NSCLC = non-small cell lung cancer
Source: Table 62, p140, Table 64, p143, Table 66, p145 of MSAC 1798 ADAR

Population 2

All the evidence for population 2 was in patients with advanced NSCLC who underwent ctDNA testing (with/without a requirement for tissue-based genetic testing to have been attempted first). None of the studies required two attempts at tissue-based testing (i.e. an uninformative initial biopsy and rebiopsy) prior to a ctDNA testing for eligibility in the study. Studies on diagnostic performance with fewer than 50 patients were excluded.

Three studies evaluated the direct impact of ctDNA testing compared to tissue-based testing on health outcomes. These investigations followed patients with NSCLC who received treatment guided by either plasma-derived or tissue-derived molecular profiling, thereby enabling a comparative assessment of the clinical effectiveness of ctDNA testing versus conventional tissue testing. A summary of the key features of the included evidence is provided in Table 13.

Table 13 Key features of the included evidence for patients with newly diagnosed NSCLC (population 2)

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Direct from test to health outcomes	Retrospective cohort studies of NSCLC patients who received ctDNA- or tissue-directed treatments.	☒ k=3 n=401	High risk of bias due to lack of adjustments for heterogeneity and confounding variables
Diagnostic performance of the test (cross-sectional accuracy) – key studies used in meta-analysis	Within-patient retrospective and prospective cohort studies	☒ k=6 n=1039	Low risk of bias as per QUADAS checklist
Change in patient management	Prospective and retrospective cohort studies, showing change in treatment received based on ctDNA testing results, change in time to treatment, and change in rebiopsy rate	☒ k=15 ^a n=15,818 ^a	Moderate risk of bias, mostly due to confounding, missing data and a heterogeneous population (also including progressed disease)
Health outcomes	A mix of studies (prospective and retrospective cohort studies, a RCT, a registry study, systematic reviews) Evidence to show the effectiveness (health outcomes) of targeted therapy vs non-targeted therapy, and health impact of more timely treatment.	☒ k=12 n=202,059	High risk of bias due to heterogeneity, uncontrolled confounding variables and inconsistencies in outcome reporting
Safety	Adverse outcomes associated with tissue biopsy and re-biopsy	☒ k=3 n=11,305	Low risk of bias

k = number of studies; n = number of patients; NSCLC = non-small cell lung cancer; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RCT = randomised controlled trial

^a excluding the numbers by Nam et al. (2021) which was a systematic review on tissue testing failure

Source: Table 25, p78, Table 30, p86, Table 37, p101-103, Table 45, p113-115 of MSC 1798 ADAR

Population 3

The majority of the evidence included for population 3 were not directly applicable to the population as defined in the ratified PICO confirmation, as ctDNA testing was used as the first-choice of test upon recurrence/progression. An independent search of the literature identified one additional relevant study that was missed by the ADAR due to inappropriately restricting the use of “NSCLC” to a Medical Subject Heading (MeSH) term rather than a free text term¹⁶. A summary of the key evidence for population 3 is included in Table 14.

¹⁶ Laufer-Geva, S, et al 2018, 'The Clinical Impact of Comprehensive Genomic Testing of Circulating Cell-Free DNA in Advanced Lung Cancer', *J Thorac Oncol*, vol. 13, no. 11, Nov, pp. 1705-1716 10.1016/j.jtho.2018.07.101.

Table 14 Key features of the included evidence for patients with recurrent/progressed NSCLC (population 3)

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Performance of the test (concordance, yield)	Within-patient comparisons or case series	☒ k=7 n=752	Moderate risk of bias – comparative evidence was not applicable
Change in patient management	Evidence to show that test result guides decisions about treatment Prospective or retrospective case series or cohorts	☒ k=7 n=3,316	Low risk of bias in studies, but low applicability in majority of studies
Predictive effect (treatment effect variation)	Retrospective analysis of RCT, comparing outcomes on osimertinib vs platinum-pemetrexed based on if variant identified on tumour tissue vs ctDNA testing	☒ k=1 n=891	Low risk of bias
Prognostic data	Prospective cohort study comparing outcomes in those with/without variant on ctDNA testing	☒ k=1 n=198	Moderate risk

k = number of studies; n = number of patients; NSCLC = non-small cell lung cancer; RCT = randomised controlled trial
Source: Table 54, p128, Table 56, p132-133, Table 50, p125 of MSAC 1798 ADAR

11. Comparative safety

No studies were identified reporting on the safety of the ctDNA testing procedure. ctDNA testing only requires a plasma sample, which can be assumed to have equivalent safety to a venous blood draw, which has manageable and minimal safety concerns (minor bruising and hematoma, with a 3.4% rate of serious complications such as phlebitis, diaphoresis, hypotension, syncope and seizure)¹⁷. The applicant claimed that ctDNA testing has non-inferior safety compared to no molecular testing (across all populations), which the commentary considered was reasonable when the direct harms of testing are considered.

The applicant also claimed that ctDNA testing has superior safety compared to a tissue rebiopsy. A systematic review and meta-analysis of the use of rebiopsy in 11 studies and 1339 patients with NSCLC reported that the overall complication rate of percutaneous transthoracic needle biopsy was 15% (95%CI 8%, 24%), with older patients being more at risk of complications than younger patients (p=0.001)¹⁸. The most common complication was pneumothorax, which occurred in 201/1142 (17.6%) of rebiopsies. The commentary therefore considered the claim of superior safety versus tissue rebiopsy to be appropriate.

The downstream consequences of using ctDNA testing in patients who would otherwise not have any molecular testing, are that more patients would potentially be eligible for targeted treatments for NSCLC. The ADAR did not consider the safety implications of downstream treatments. Targeted therapies such as EGFR-TKIs are associated with a different safety profile to non-targeted therapies, but these safety implications are usually considered manageable. The commentary considered an overall claim of non-inferior safety was likely appropriate.

¹⁷ Galena, HJ 1992, 'Complications occurring from diagnostic venipuncture', *J Fam Pract*, vol. 34, no. 5, May, pp. 582-584

¹⁸ Nam, BD, et al 2021, 'Tissue Adequacy and Safety of Percutaneous Transthoracic Needle Biopsy for Molecular Analysis in Non-Small Cell Lung Cancer: A Systematic Review and Meta-analysis', *Korean J Radiol*, vol. 22, no. 12, Dec, pp. 2082-2093 10.3348/kjr.2021.0244.

12. Comparative effectiveness

Population 1

Direct from test to health outcomes evidence

No direct evidence was identified linking testing in those suspected of having NSCLC, through to health outcomes. A linked evidence approach was used in the ADAR, linking together the yield of testing, the test success rate, the proportion of cases treated based on findings from ctDNA testing, and a small amount of health outcomes in those treated. The commentary also included an analysis of the proportion of non-NSCLC cases who were identified with clinically actionable variants, and the overall probability that an actionable variant would therefore indicate that the patient has NSCLC.

Linked evidence – Test performance

Yield of actionable alterations

Five studies compared the yield of actionable variants identified by ctDNA testing with/without a comparison against the yield of actionable variants identified by testing of tumour tissue (Table 15). The yield was similar between testing methods. The proportion of patients identified with actionable variants from each testing method, as reported by Garcia-pardo et al. (2023), was used as a key input for the economic evaluation in population 1.

Table 15 Yield of actionable alterations in suspected NSCLC

Study ID	Yield of ctDNA testing	Yield of tissue testing
Yang 2023 ¹⁹	Guideline-recommended: 76/180 (42.2%) 114 diagnosed/180 suspected Of those with 122 metastatic NSCLC:	Guideline-recommended: 67/180= 37.2%
Garcia-pardo 2022 ²⁰	Actionable alterations: 4/20 (20%) actionable alterations out of <i>EGFR</i> , <i>ALK</i> , <i>ERBB2</i> , <i>MET</i> , <i>RET</i> , <i>KRAS</i> , <i>BRAF</i>	Actionable alterations: 7/20 (35%) actionable alterations out of <i>EGFR</i> , <i>ALK</i> , <i>ERBB2</i> , <i>MET</i> , <i>RET</i> , <i>KRAS</i> , <i>BRAF</i>
Garcia-pardo 2023 ²¹	Actionable alterations: 33*/150 (22%) *28 <i>EGFR</i> , 2 <i>ALK</i> , 1 <i>ROS1</i> , 2 <i>MET</i>	Actionable alterations: 31*/145 (21.4%) *25 <i>EGFR</i> , 4 <i>ALK</i> , 1 <i>ROS1</i> , 1 <i>MET</i> Only 145 had biopsy
Cui 2022a ²²	Guideline-recommended: 30/49 (61%) Of 49 patients with evaluable samples, 30 had AMP/ASCO/CAP tier 1 variants including 20 additional tier 1 variants compared to tissue testing. Three patients with non-informative cfDNA-NGS had tier 1 variants identified on tissue testing.	NR
Cheng 2021 ²³	Clinically relevant: 9 of 20 (45%) Defined as those guiding standard or investigational targeted therapy options or enabling completion of genotyping.	NR

ALK = ALK receptor tyrosine kinase; AMP = Association for Molecular Pathology; ASCO = American Society of Clinical Oncology; BRAF = B-Raf proto-oncogene, serine/threonine kinase; CAP = College of American Pathologists; cfDNA = cell-free deoxyribonucleic acid; EGFR = epidermal growth factor receptor; ERBB2 = erb-b2 receptor tyrosine kinase 2; ID = identification; KRAS = KRAS proto-oncogene, GTPase; MET = MET proto-oncogene, receptor tyrosine kinase; NGS = next-generation sequencing; NR = not reported; NSCLC = non-small cell lung cancer; RET = ret proto-oncogene; ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase
Source: Table 63, p141 MSAC 1798 ADAR

The ADAR did not present concordance data between testing methods specific for population 1, claiming that the data addressed for population 2 would be applicable. The commentary considered that the yield of actionable variants would be lower in those suspected of having NSCLC, compared to those with NSCLC, and this would alter the positive predictive value (PPV) and negative predictive value (NPV) results between populations. Garcia-pardo et al. (2022) provided sufficient data to allow concordance to be assessed, so this was extracted during the commentary. The positive percent agreement between ctDNA testing and tumour tissue testing was 57.1% (4/7), and the negative percent agreement was 92.3% (12/13). The PPV was 80%, meaning that 20% of those identified on ctDNA testing, did not have any variants detected by tumour tissue. It was unclear whether these cases should be considered “false positives” due to clonal haematopoiesis, or whether they reflect “false negatives” by tumour tissue.

¹⁹ Yang, CY et al 2023, 'Upfront liquid next-generation sequencing in treatment-naïve advanced non-small cell lung cancer patients: A prospective randomised study in the Taiwanese health system', *Eur J Cancer*, vol. 193, Nov, p. 113310 10.1016/j.ejca.2023.113310.

²⁰ Garcia-Pardo, M, et al 2022, 'Plasma-first: accelerating lung cancer diagnosis and molecular profiling through liquid biopsy', *Ther Adv Med Oncol*, vol. 14, p. 17588359221126151 10.1177

²¹ Garcia-Pardo, M, et al 2023, 'Association of Circulating Tumor DNA Testing Before Tissue Diagnosis With Time to Treatment Among Patients With Suspected Advanced Lung Cancer: The ACCELERATE Nonrandomized Clinical Trial', *JAMA Netw Open*, vol. 6, no. 7, Jul 3, p. e2325332 10.1001/jamanetworkopen.2023.25332.

²² Cui, Wet al 2022, 'A pilot of Blood-First diagnostic cell free DNA (cfDNA) next generation sequencing (NGS) in patients with suspected advanced lung cancer', *Lung Cancer*, vol. 165, Mar, pp. 34-42 10.1016/j.lungcan.2022.01.009.

²³ Cheng, ML, et al 2021, 'Plasma cfDNA Genotyping in Hospitalized Patients With Suspected Metastatic NSCLC', *JCO Precis Oncol*, vol. 5, Nov, pp. 726-732 10.1200/PO.21.00029.

The ADAR claimed that there was a high level of concordance between those suspected of having NSCLC, and those confirmed to have it. The commentary calculated that the proportion of patients suspected of having advanced NSCLC, being diagnosed with advanced NSCLC based on pathological diagnosis, was 251/364²⁴ (69.0%, range 60% to 71.6%) (Table 16).

Two studies reported on the variants identified across all patients tested by ctDNA testing (not only those confirmed to have NSCLC). One small study (Garcia-pardo et al. 2022) reported that of 20 patients suspected of having lung cancer, only 4 were identified to have actionable alterations using a DNA-based ctDNA panel (i.e. fusions were not tested in plasma), and none of the alterations were in patients not diagnosed with NSCLC. In another study, Cheng et al. (2021) reported that 1/5 patients with non-NSCLC diagnoses were identified with actionable variants, as one patient had a *BRAF* V600K variant. Note, in Australia, targeted therapy for patients with NSCLC and a *BRAF* V600E variant is recommended for PBS-listing, but not *BRAF* V600K, so it may not be considered actionable in the Australian healthcare setting. If this variant is considered noninformative (for the treatment of NSCLC), then the positive predictive value (the proportion of cases with a clinically actionable variant who are actually found to have NSCLC) is 100%.

No evidence was presented in the ADAR on the frequency of *EGFR* activating variants or T790M variants, *ALK* or *ROS1* gene rearrangements, *MET*ex14 skipping alterations, *NTRK* or *RET* gene fusions, *BRAF* V600E variants in cancer types other than NSCLC. Although the two small studies included in the ADAR did not identify any of these variants in non-NSCLC diagnoses, the potential for this to happen cannot be ruled out.

The certainty of evidence was assessed (GRADE: ⊕⊕⊕⊖). Certainty was downgraded due to imprecision, with a high degree of variability between studies.

²⁴ Based on Cheng 2021 (13/19), Garcia-Pardo 2022 (12/20), Garcia-Pardo 2023 (104/145), and Yang (122/180).

Table 16 Variants identified by ctDNA testing (and tissue) based on pathological diagnosis (table compiled during the evaluation)

Study ID	Population	Diagnosis after tissue-based testing	Variants identified by ctDNA testing
Cheng 2021	N=19 patients with clinically suspected metastatic NSCLC (who were evaluable – excluding one patient who died prior to biopsy)	13/19 (68.4%) confirmed metastatic NSCLC 1 early-stage NSCLC coinciding with another solid tumour	9/19 with actionable alterations in <i>EGFR</i> or <i>KRAS</i> genes
		1 melanoma	<i>BRAF</i> V600K
		1 breast cancer	Variant without targeted therapy for NSCLC
		1 small cell lung cancer	Variant without targeted therapy for NSCLC
		1 spindle cell neoplasm	Variant without targeted therapy for NSCLC
		1 benign condition	-
	Total participants: 18/19 with cancer of some description, 13 of which were metastatic NSCLC	10 with variants associated with NSCLC, only 9 of which actually had it	
Garcia-pardo 2022	20 patients suspected of advanced lung cancer	12/20 (60%) lung adenocarcinoma	4/20 (20%) actionable alterations on ctDNA testing
		5 lung non-adenocarcinoma 3 non-lung cancer (1 carcinoma of unknown primary, 1 gastric adenocarcinoma, 1 diffuse B-cell lymphoma).	No alterations detected
Garcia-pardo 2023	145 patients suspected of advanced lung cancer based on imaging and underwent tissue biopsy	104/145 (71.7%) confirmed advanced or unresectable NSCLC	Actionable alterations: 33*/150 (22%) *28 <i>EGFR</i> , 2 <i>ALK</i> , 1 <i>ROS1</i> , 2 <i>MET</i>
		3 stage IA NSCLC 14 SCLC 18 not lung cancer 6 negative biopsy (3 insufficient tissue, 2 pleural fluid inflammatory or benign, 1 organising pneumonia)	Not stated
Yang 2023	N=180 with suspicion of advanced NSCLC	122 Metastatic NSCLC (67.8%)	Actionable alterations: 56 cases ctDNA testing + tissue+ 20 cases ctDNA testing + / tissue -
		14 stage I-IIIa NSCLC 10 benign disease 9 other cancer type 13 small cell lung cancer 12 not reported (due to lack of treatment or insufficient ctDNA)	Not stated

ALK = ALK receptor tyrosine kinase; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; ctDNA = circulating tumour deoxyribonucleic acid; *EGFR* = epidermal growth factor receptor; ID = identification; *KRAS* = KRAS proto-oncogene, GTPase; *MET* = MET proto-oncogene, receptor tyrosine kinase; N = number of studies; NSCLC = non-small cell lung cancer; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase; SCLC = small cell lung cancer

Source: created during the commentary

Linked evidence – Change in management

The ADAR included three studies on the impact of ctDNA testing on management (Table 17). Cheng et al. (2021) was unclear whether patients were treated before or after pathological diagnoses were received. However, Cui et al. (2022a) reported that 11/49 (22%) patients tested with ctDNA testing and had evaluable results had targeted therapy initiated on the basis of NGS on ctDNA testing. A further 6 patients (15%) had variants identified without targeted treatment options and commenced chemotherapy and/or immunotherapy prior to receiving tissue molecular results.

The certainty of evidence was assessed (GRADE: ⊕⊖⊖⊖). Certainty was downgraded due to imprecision given small patient numbers.

Table 17 Change in treatment in clinically suspected NSCLC receiving ctDNA testing NGS

Study	Population	Change in management (treatment with targeted therapy)
Cheng 2021	N=19 with clinically suspected NSCLC, 9 with actionable alterations	Proportion of positive test: 3*/9 (33.3%) Proportion of clinically suspected NSCLC: 3/19 (15%) *one patient with melanoma n=1 was removed
Cui 2022a	N=49 clinically suspected NSCLC	Proportion of positive test: NR Proportion of clinically suspected NSCLC: 11/49 (22%) (95% CI: 12, 27%)
Yang 2023	N=180 with suspicion of advanced NSCLC, 20 with ctDNA-positive/tissue negative discordant results	Proportion of positive test: 9/20 (45%) Proportion of clinically suspected NSCLC: Cannot be calculated

CI = confidence interval; N = number of studies; n = number of patients; NGS = next-generation sequencing; NR = not reported; NSCLC = non-small cell lung cancer
Source: Table 65, p144 MSAC 1798 ADAR

Linked evidence – Health outcomes (impact of change in management)

Treatment effectiveness

A single study was identified in the ADAR that assessed health outcomes in 391 patients who were clinically diagnosed with advanced lung cancer without a tissue biopsy (the CHALLENGE trial) (Table 18). Of these, 140 were identified as having *EGFR* sensitising variants based on ctDNA testing. These patients were treated with icotinib (a first-line *EGFR*-TKI that is not PBS-listed, but may be considered to have equivalent efficacy to erlotinib, gefitinib and afatinib²⁵, so results are likely applicable to treatments available in Australia). Results were compared to the CONVINCENCE trial, which compared outcomes resulting from icotinib versus cisplatin/pemetrexed in patients with *EGFR* variants, identified using tumour tissue. Health outcomes in the CHALLENGE study were slightly worse than the icotinib arm in the CONVINCENCE trial, and was hypothesised in the ADAR that this was likely due to prognostic differences between the patient samples, with the patients in the CHALLENGE trial being slightly older, and with a poorer performance status than those enrolled in the CONVINCENCE trial. Thus far, no evidence has been identified of *EGFR* sensitising variants having been identified in cases suspected of having NSCLC, who have not been confirmed to have NSCLC, if pathological testing is feasible. The commentary considered the conclusions of the ADAR are therefore reasonable, that the differences in results are likely

²⁵ Liang, W, et al 2014, 'Network meta-analysis of erlotinib, gefitinib, afatinib and icotinib in patients with advanced non-small-cell lung cancer harboring EGFR mutations', *PLoS One*, vol. 9, no. 2, p. e85245 10.1371/journal.pone.0085245.

due to prognostic differences, rather than due to a portion of patients being treated, who do not actually have NSCLC.

The certainty of evidence was assessed (*GRADE*: ⊕⊕⊕⊖). Certainty was downgraded due to inconsistencies due to long 95% confidence interval for overall survival (OS) between groups.

Table 18 Linked-health outcomes in suspected NSCLC (identified with *EGFR* variant on ctDNA testing)

Study ID	ORR	PFS	OS	DCR
Xu et al 2022 ²⁶	52.6% (95% CI 43.1, 61.9%)	10.3 months (95% CI 8.3, 12.2)	23.2 months (95% CI 17.7, 28.0)	84.5% (95% CI 76.6%, 90.5%)

CI = confidence interval; DCR = disease control rate; *EGFR* = epidermal growth factor receptor; ID = identification; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival
Source: Table 66, p145 MSAC 1798 ADAR

Clinical claim

The commentary considered that the limited evidence available for population 1 suggested that ctDNA testing does identify clinically actionable variants in patients suspected of having NSCLC and changes the probability that the person has NSCLC from 69% to potentially up to 100%. If restrictions for targeted treatments for NSCLC are altered to become available to those without confirmed pathological diagnosis, it is unlikely that many (or any) patients would receive inappropriate targeted therapy. Those who receive targeted therapy due to having clinically actionable variants, are likely to have superior health outcomes to patients who do not undergo ctDNA testing. Those without clinically actionable variants are unlikely to benefit from having undergone a ctDNA testing, but the harms with testing (having venipuncture to retrieve a small amount of blood) are minimal. If patients with a cancer other than NSCLC are treated with targeted therapies due to being identified with clinically actionable variants, it is unknown what the effectiveness of these therapies would be, (a) compared to what the patient would have received in the absence of ctDNA testing and (b) compared to that for histologically confirmed diagnosis of a target lesion.

In patients suspected of having NSCLC (population 1), the applicant claimed that use of ctDNA testing was superior in effectiveness and non-inferior in safety compared to no molecular testing. This commentary considered that this claim is dependent on targeted therapies being made available to patients without a confirmed tissue-based diagnosis. The commentary considered that if the targeted therapies are made available, then effectiveness would be superior compared to no molecular testing, and non-targeted treatment. The safety outcomes differ between targeted therapies and non-targeted therapies, but a conclusion of non-inferior safety is likely reasonable.

²⁶ Xu, J, Liu, et al 2022, 'Evaluation of Clinical Outcomes of Icotinib in Patients With Clinically Diagnosed Advanced Lung Cancer With *EGFR*-Sensitizing Variants Assessed by Circulating Tumor DNA Testing: A Phase 2 Nonrandomized Clinical Trial', *JAMA Oncol*, vol. 8, no. 9, Sep 1, pp. 1328-1332 10.1001/jamaoncol.2022.2719.

Population 2

Direct from test to health outcomes evidence

The ADAR presented two studies that directly compared progression-free survival (PFS) and/or OS between patients receiving plasma test-directed therapy and those receiving tissue test-directed therapy^{27,28} (Table 19).

Evidence from Raez et al. (2023) and Tran et al. (2021) suggests that ctDNA testing-directed therapy yields progression-free survival (PFS) outcomes comparable to those of tissue-directed therapy in patients with advanced NSCLC, with no statistically significant differences observed. However, the Raez study's methodology—particularly its retrospective classification of the "informative" test based on which result was available first—introduces potential bias, compounded by faster turnaround times for plasma testing. These limitations, along with heterogeneity in patient populations and critical risk of bias, contribute to low certainty in the evidence (GRADE: ⊕⊖⊖⊖). The findings align with previous research indicating that health outcomes may be more reflective of baseline patient characteristics than the diagnostic modality itself, underscoring the need for cautious interpretation.

Table 19 Median PFS and OS between patients treated based on ctDNA versus tissue biopsy NGS results

Study ID	N	Context	Treatment	Plasma-directed therapy (range)	Tissue-directed therapy (range)	Absolute difference (plasma – tissue) (p-value)	ctDNA to tissue hazard ratio (95% CI)
Progression-free survival							
Raez 2023	N=135 with PFS data Unclear how many in the ctDNA-guided treatment group or the tissue-guided treatment arm	Patients retrospectively categorised based on patient records according to test availability, TAT and detection of actionable alteration All included patients had stage IV NSCLC.	Treatment not defined	43 months	46 months	-3 months (p = 0.9847)	0.99 (0.57, -1.60)
Tran 2021	N=80 (40 tissue, 40 plasma)	Consecutive cohort of 40 patients who received EGFR-TKI based on either ctDNA or tissue testing results.	EGFR-TKI	379 days (118–1266)	353 days (115–919 days)	26 days (p = 0.42)	1.21 (0.77-1.88)
Overall survival							

²⁷ Tran, HT, et al 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', *JCO Precis Oncol*, vol. 5, Aug, 10.1200/po.20.00532.

²⁸ Raez, LE, et al 2023, Liquid Biopsy Versus Tissue Biopsy to Determine Front Line Therapy in Metastatic Non-Small Cell Lung Cancer (NSCLC)', *Clin Lung Cancer*, vol. 24, no. 2, Mar, pp. 120-129 10.1016/j.clc.2022.11.007.

Study ID	N	Context	Treatment	Plasma-directed therapy (range)	Tissue-directed therapy (range)	Absolute difference (plasma – tissue) (p-value)	ctDNA to tissue hazard ratio (95% CI)
Raez 2023	N=129 with OS data Unclear how many in the ctDNA-guided treatment group or the tissue-guided treatment arm	Patients retrospectively categorised based on patient records according to test availability, TAT and detection of actionable alteration	Treatment not defined	Not reached	82 months	N/A ($p = 0.8322$)	0.94 (0.50, –1.74)

CI = confidence interval; *EGFR* = epidermal growth factor receptor; ID = identification; N = number of studies; N/A = not applicable; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; TAT = turnaround time; TKI = tyrosine kinase inhibitor
Source: Table 26, p80, MSAC 1789 ADAR

Mack et al. (2020) was the only study to report comparative objective response rates (ORR) to targeted therapies based on ctDNA- versus tissue-directed treatment. Due to limited clinical outcomes data (n=12) for ctDNA -directed therapy in this study, a pooled analysis of 10 additional studies (n=174) of published literature was conducted in the ADAR. The pooled ORRs showed no statistically significant difference between ctDNA and tissue testing ($p > 0.12$); however, the indirect comparison across heterogeneous patient cohorts and lack of adjustment for confounding variables limit the validity of the findings. The certainty of evidence was rated as very low (GRADE: ⊕⊖⊖⊖), primarily due to critical risk of bias and imprecision. These results, based on a small and heterogeneous population, suggest no meaningful difference in health outcomes between testing methods, though conclusions remain highly uncertain.

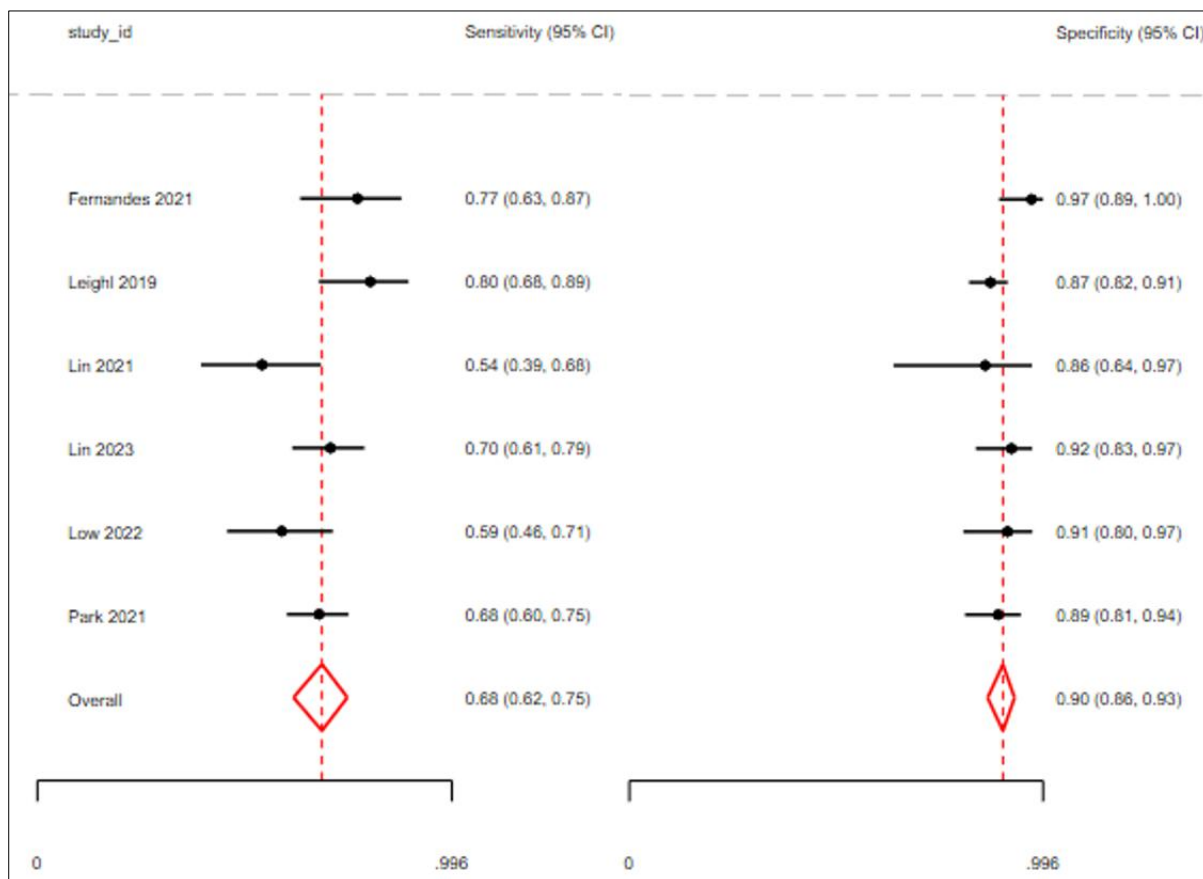
However, as this population is restricted to newly diagnosed NSCLC patients whose initial tissue biopsy was insufficient for tissue-based testing or who failed tissue-based testing, the alternative to ctDNA testing would be no molecular testing. No direct evidence on targeted treatment after ctDNA testing in NSCLC compared to standard of care (no molecular testing and standard treatment) was presented in this ADAR.

Linked evidence – Test performance

Test performance

Of the 24 studies reviewed, ten studies were identified (9 studies in the ADAR and one during the commentary) that reported overall concordance data comparing ctDNA testing NGS to tissue NGS. The remaining 15 studies provided gene-level concordance data, enabling meta-analysis of sensitivity and specificity stratified by type of testing used. While some studies focused on actionable biomarkers, others included clinically relevant variants without available targeted therapies. The meta-analysis on overall concordance demonstrated high negative percent agreement (specificity) (0.89, 95% CI: 0.83, 0.93) and moderate positive percent agreement (sensitivity) (0.68, 95% CI: 0.56, 0.75) for ctDNA testing NGS in detecting actionable variants. A commentary-stage meta-analysis which included slightly different data/studies than the analysis done in the ADAR yielded nearly identical results (negative percent agreement (specificity): 0.90; 95%CI 0.86, 0.93), positive percent agreement (sensitivity): 0.68; 95%CI 0.62, 0.75) (Figure 1).

Figure 1 Forest plot of sensitivity (positive percent agreement) and specificity (negative percent agreement) of ctDNA NGS compared to tissue NGS



CI = confidence interval; NGS = next generation sequencing.
 Source: plotted during the commentary

Yield of actionable alterations

Ten studies provided sufficient data to calculate the yield of actionable or clinically relevant genomic alterations using ctDNA testing NGS, defined as the proportion of successfully tested patients with identified alterations^{5,29,32, 36 ,40, 38, 51, 30, 50, 31}. Yields ranged from 27.2% to 29.1% for actionable variants and up to 48% when including clinically relevant alterations. Comparisons with tissue testing showed variable yields (30–69%), influenced by testing modality and patient factors such as tumour heterogeneity and sample quality. Notably, studies like Mack et al. (2020) and Aggarwal et al. (2019) demonstrated that ctDNA testing can reliably detect actionable variants, even in patients without tissue testing, supporting its utility as an alternative when tissue samples are unavailable. However, limitations such as small sample sizes, inconsistent definitions of actionable variants, and heterogeneity across studies contribute to only moderate certainty in the evidence (GRADE: ⊕⊕⊖⊖). Furthermore, some studies Aggarwal

²⁹ Aggarwal, C, et al 2019, 'Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer', *JAMA Oncol*, vol. 5, no. 2, Feb 1, pp. 173-180 10.1001/jamaoncol.2018.4305
³⁰ Palmero, R, et al 2021, 'Biomarker Discovery and Outcomes for Comprehensive Cell-Free Circulating Tumor DNA Versus Standard-of-Care Tissue Testing in Advanced Non-Small-Cell Lung Cancer', *JCO Precis Oncol*, vol. 5, no. (Palmero, Nadal) ICO Bellvitge, Hospitalet Llobregat, Spain(Taus) Hospital del Mar, Barcelona, Spain(Taus) Universidad Autonoma de Barcelona (UAB), Barcelona, Spain(Viteri) Quiron Salud-Dexeus University Institute, IOR, Medical Oncology Department, Barcel, Nov, pp. 93-102. 10.1200/PO.20.00241
³¹ Pritchett, MA, et al 2019, 'Prospective Clinical Validation of the InVisionFirst-Lung Circulating Tumor DNA Assay for Molecular Profiling of Patients With Advanced Nonsquamous Non-Small-Cell Lung Cancer', *JCO Precis Oncol*, vol. 3, 10.1200/po.18.00299

et al 2019.³² included a significant percentage (7% to 48%) of patients who weren't newly diagnosed (either confirmed to be on second- or third-line treatment, or with confirmed disease progression (on treatment) at the time of plasma NGS genotyping).

Test success rate

Five studies reported test success rates for ctDNA testing NGS and tissue-based testing in NSCLC^{29,38,50,5,31}, with plasma-based testing consistently achieving higher success rates (98–100%) compared to tissue testing (60–88%). Tissue test failures were primarily due to insufficient sample quantity (e.g. due to small or inaccessible tumours, low tumour cellularity, advanced disease with poor performance status, prior treatments, or the biopsy method used), while ctDNA testing failures were attributed to issues such as sample contamination or low diversity. Some studies also reported circulating tumour DNA (ctDNA) detection rates in plasma, ranging from 75–95%^{5, 50, 38}, though absence of ctDNA did not indicate test failure. In matched cohorts, ctDNA testing demonstrated superior reliability, particularly in patients unable to undergo tissue biopsy. However, the certainty of evidence was rated as moderate (*GRADE*: ⊕⊕⊖⊖), due to retrospective study designs and potential selection bias. The ADAR states that overall, ctDNA testing NGS offers a more feasible alternative to tissue testing in clinical practice.

It is unknown what proportion of patients would have been excluded from these studies due to being considered ineligible for tumour biopsy (e.g. due to poor health of the patient or due to location of the tumour).

Turnaround time

Across six studies comparing turnaround times (TAT) between ctDNA testing NGS and traditional tissue testing, ctDNA testing consistently demonstrated faster results^{5,22,38, 28, 52, 35}. Five of the six studies reported statistically significant differences ($p < 0.05$), with ctDNA testing TAT ranging from 8 to 10.5 days, compared with 15 to 31 days for tissue testing. However, variability in how TAT was defined and measured across studies introduced potential bias. Some studies measured TAT from test ordering to result receipt, while others began timing from sample collection, often biasing results in favour of tissue testing. Despite these inconsistencies, studies that standardised measurement from test ordering (e.g., Cui et al. (2022c), Leighl et al. (2019), Raez et al. (2023) found ctDNA testing to be faster by 6 to 21 days ($p < 0.001$).

The certainty of this evidence was rated as moderate (*GRADE*: ⊕⊕⊕⊖). downgraded due to inconsistent TAT definitions and prolonged intervals between sample collections. Additionally, none of the studies accounted for patient-level factors or multivariate analyses that could influence TAT. The findings align with existing literature and clinical guidelines supporting ctDNA testing for expedited results, especially when tissue testing delays are anticipated. However, data for population 2 and population 3 were combined in the ADAR, and it is unclear whether the TAT would differ between these populations. It is unclear how applicable these results are if patients are required to have a rebiopsy attempt (if feasible), prior to being eligible for ctDNA testing.

Linked evidence – Change in management

Time to treatment initiation

The ADAR presented two studies – Cui et al. (2022c) and Page et al. (2022) – that reported the comparative time to treatment initiation (TTI) for patients undergoing ctDNA testing NGS versus tissue testing. Both studies found that ctDNA testing significantly reduced TTI, with median times of 16–18 days compared to 31–35 days for tissue testing ($p < 0.005$). Cui et al. measured TTI

³² Zatarain-Barrón, ZL, et al 2021, 'Cell-Free Circulating Tumor DNA Improves Standard Genotyping of Non-Small-Cell Lung Cancer and Increases Detection of Targetable Alterations in a Selected Hispanic Cohort', *Oncology*, vol. 99, no. 8, pp. 539-546 10.1159/000514648.

from the date of sample collection to the start of first-line systemic treatment, while Page et al. measured from test ordering to initiation of targeted therapy. Despite differences in healthcare systems (United Kingdom, UK and United States, US), both studies reflected real-world clinical practice and logistical variability.

Although neither study was conducted in Australia, the ADAR considered the results to be applicable due to similarities in healthcare infrastructure and diagnostic pathways. In particular, the UK study aligns with Australian practices such as reflex tissue testing following biopsy. The certainty of evidence was rated as low to moderate (GRADE: ⊕⊕⊖⊖), primarily due to variability in protocols. Furthermore, there was a lack of data on patients requiring rebiopsy attempts before ctDNA testing eligibility. These (albeit limited evidence) findings support the use of ctDNA testing to expedite treatment initiation, especially in settings where delays in tissue testing are common.

Change in treatment due to ctDNA testing

The evidence for 'change in management' was included in the ADAR if decisions were made based on ctDNA testing NGS in patients who either did not undergo tissue testing or had negative tissue results. Across 13 studies (12 identified in the ADAR^{22, 29, 4, 31, 5, 33, 52, 32, 34, 28, 35, 36} and one during the commentary¹⁶), ctDNA testing identified actionable alterations in approximately 30% of tested patients, with similar detection rates in those lacking tissue samples. Nine studies reported changes in management based solely on plasma testing, with targeted therapy initiated in 18–44% of patients, however, most studies reported targeted therapy in around 20% (18.2% - 22%) of patients^{29, 31, 16, 37}. Notably, Mack et al. (2020; n=252) found that 50% of patients with actionable variants received targeted therapy, though half had *KRAS* variants, which lacked approved treatments at the time.

Three studies^{28, 35, 36} examined cases with discordant results—ctDNA-positive but tissue-negative—showing treatment changes in 43–75% of newly diagnosed NSCLC patients. For example, Sugimoto et al. (2023) reported that 20 of 46 discordant patients received targeted therapy. Raez et al. (2023) emphasized the impact of turnaround time, with 73.5% of treatment decisions guided by plasma testing simply because results were available sooner. These findings support the role of ctDNA testing as a viable alternative when tissue is unavailable or delayed, though applicability may be limited for patients requiring multiple biopsy attempts before ctDNA testing eligibility.

The treatment changes based on ctDNA testing results would be applicable to the Australian healthcare setting, assuming that current PBS-restrictions for targeted therapies for patients with NSCLC are amended to allow for the targeted variant to be identified by ctDNA testing. This aligns with the eligibility criteria outlined in proposed item descriptor DDDD. However, it remains unclear whether ctDNA testing influences other aspects of patient management (as suggested in descriptor CCCC).

³³ Bustamante Alvarez, J et al 2021, 'Treatment of Non-Small-Cell Lung Cancer Based on Circulating Cell-Free DNA and Impact of Variation Allele Frequency', *Clin Lung Cancer*, vol. 22, no. 4, Jul, pp. e519-e527. 0.1016/j.clc.2020.11.007

³⁴ Lin YT, et al 2024. Tissue or liquid rebiopsy? A prospective study for simultaneous tissue and liquid NGS after first-line EGFR inhibitor resistance in lung cancer. *Cancer Med* 13(1): e6870.

³⁵ Sehayek O, et al 2022. Liquid First Is "Solid" in Naive Non-Small Cell Lung Cancer Patients: Faster Turnaround Time With High Concordance to Solid Next-Generation Sequencing. *Front Oncol* 12((Sehayek, Zemel) Ben-Gurion University, Be'er Sheva, Israel (Kian, Roisman, Peled) The Institute of Oncology, Shaare Zedek Medical Center, Jerusalem, Israel(Onn, Stoff, Sorotsky, Bar) Sheba Medical Center, Ramat Gan, Israel (Dudnik) Soroka Medical Center, B): 912801.

³⁶ Sugimoto A, et al 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). *Clin Cancer Res* 29(8): 1506-1514.32

³⁷ Cui, W, et al 2022, 'Up-front cell-free DNA next generation sequencing improves target identification in UK first line advanced non-small cell lung cancer (NSCLC) patients', *Eur J Cancer*, vol. 171, Aug, pp. 44-54 10.1016/j.ejca.2022.05.012.

Several studies included patients with progressed disease, which may affect generalisability to newly diagnosed populations. The variability in treatment uptake reflects the influence of additional factors beyond biomarker status, such as patient preferences, comorbidities, the Eastern Cooperative Oncology Group (ECOG) performance status, socioeconomic barriers, and tumour characteristics. The certainty of evidence was rated as moderate (GRADE: ⊕⊕⊕⊖), acknowledging these confounding variables.

Rebiopsy avoided

Plasma-based genomic testing shows a near-perfect success rate, in contrast to tissue-based NGS, which has a variable success rate between 62% and 88%. The most common cause of tissue testing failure is insufficient tissue quantity, accounting for 62% to 79.7% of failures^{29,31,38}. The ADAR claimed that tissue insufficiency affects approximately 6.5%³⁹ to 33% of NSCLC patients, potentially necessitating re-biopsy, although the 33% result was not able to be verified during the commentary.

Feasibility of re-biopsy is influenced by tumour characteristics and patient-specific factors, such as location, size, and overall health. While the ADAR identified limited data on re-biopsy rates, one case series (Li et al. 2021) reported that among patients with tissue testing failure due to insufficiency, 86.7% avoided re-biopsy by undergoing ctDNA testing NGS, with only 13.3% requiring repeat procedures. These findings underscore the clinical value of ctDNA testing in mitigating procedural risks and delays associated with tissue re-biopsy, although the certainty of evidence remains low to moderate (GRADE: ⊕⊕⊖⊖) due to study design limitations.

The applicability of this evidence is contingent upon the restrictions placed on the use of ctDNA testing. If ctDNA testing is restricted to cases where rebiopsy is either not possible or has already failed—as recommended by PASC—its potential to reduce the overall number of tissue rebiopsies would be limited. Under such constraints, ctDNA testing would primarily serve as a fallback option rather than a proactive alternative to tissue sampling.

Linked evidence – Health outcomes

Comparative effectiveness of targeted vs non-targeted therapies in patients with NSCLC

The ADAR presented evidence on PFS and OS in patients who underwent ctDNA testing, however this evidence lacked a comparator and therefore it is difficult to interpret these results. The comparative evidence of the effectiveness of targeted versus non-targeted therapy in patients with NSCLC is presented below.

Four studies included in the ADAR consistently presented an improvement in clinical outcomes in patients with actionable genomic alterations in NSCLC who underwent targeted therapies, compared to non-targeted treatments. For instance, Bonanno et al. (2020)⁴⁰ and Scott et al. (2024)⁴¹ showed that patients receiving plasma-directed targeted therapy had superior OS

³⁸ Leighl, NB, et al 2019, 'Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non-small Cell Lung Cancer', *Clin Cancer Res*, vol. 25, no. 15, Aug 1, pp. 4691-4700 10.1158/1078-0432.Ccr-19-0624.

³⁹ Nam, BD, et al 2021, 'Tissue Adequacy and Safety of Percutaneous Transthoracic Needle Biopsy for Molecular Analysis in Non-Small Cell Lung Cancer: A Systematic Review and Meta-analysis', *Korean J Radiol*, vol. 22, no. 12, Dec, pp. 2082-2093 10.3348/kjr.2021.0244.

⁴⁰ Bonanno, L, et al 2020, 'Clinical Impact of Plasma and Tissue Next-Generation Sequencing in Advanced Non-Small Cell Lung Cancer: A Real-World Experience', *Oncologist*, vol. 25, no. 12, Dec, pp. e1996-e2005 10.1634/theoncologist.2020-0148.

⁴¹ Scott, JA et al 2024, 'Compromised Outcomes in Stage IV Non-Small-Cell Lung Cancer With Actionable Mutations Initially Treated Without Tyrosine Kinase Inhibitors: A Retrospective Analysis of Real-World Data', *JCO Oncol Pract*, vol. 20, no. 1, Jan, pp. 145-153 10.1200/OP.22.00611.

compared to those receiving empirical or non-targeted therapies. Bonanno et al. reported a median OS that was not reached in the targeted group versus 9.1 months in the non-targeted group ($p = 0.046$), while Scott et al. found a median OS of 28.8 months versus 16.5 months, respectively. Klarenbeek et al. (2023)⁴², using a large national registry, further confirmed these findings (Table 20). Zatarain-Barron et al. (2021) showed that a smaller population who had actionable variants identified on ctDNA testing yielded a median OS of 40.2 months with targeted therapy compared to 22.3 months for those who stayed on non-targeted therapy.

Additionally, Bonanno et al. highlighted that patients with actionable variants who received immunotherapy instead of targeted therapy had inferior outcomes, reinforcing the importance of biomarker-driven treatment selection. Hoang et al. (2020)⁴³ conducted a network meta-analysis ($K = 128$, $N = 39,501$), which supported the superiority of targeted therapies over chemotherapy in terms of objective response rate (ORR) and PFS, with consistent results across Bayesian and frequentist analyses. These findings align with PBAC submissions for currently listed targeted therapies (e.g. erlotinib, gefitinib, afatinib, osimertinib, crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, entrectinib, tepotinib, selpercatinib, larotrectinib) and clinical guidelines (e.g., NCCN 2025⁴⁴), which recommend targeted therapies as first-line treatment in eligible patients due to their higher efficacy. The certainty of evidence was rated as moderate (GRADE: ⊕⊕⊕⊖).

Table 20 Overall survival in NSCLC patients on targeted vs non-targeted therapy

Study	Population	Comparison	Targeted therapy Median OS in months (95% CI)	Non- targeted therapy Median OS in months (95% CI)	Key Findings
Bonanno et al. (2020)	N = 235 advanced NSCLC patients with actionable variants	Targeted therapy vs. non-targeted therapy	Not reached	9.1 (4.6, 13.6)	Targeted therapy significantly improved OS; immunotherapy inferior in this group ($p = 0.046$)
Scott et al. (2024)	N=501 NSCLC patients with actionable variants	Targeted therapy vs. non-targeted therapy	28.8 (23.3, 34.6)	16.5 (12.2, 21.7)	Targeted therapy associated with significantly better OS
Klarenbeek et al. (2023)	N = 10,306 stage III/IV NSCLC patients from national registry (Netherlands)	Targeted vs. non-targeted therapy	1 year: 61% 3 years: 31% 5 years: 14%	1 year: 44% 3 years: 16% 5 years: 9%	Targeted therapy improved OS across 1-, 3-, and 5-year follow-up
Zatarain-Barron et al. (2021)	N = 54 stage III/IV NSCLC patients enrolled to receive ctDNA testing	Targeted vs. non-targeted therapy	40.2 (27.1, 53.6)	22.3 (8.3, 36.5)	Targeted therapy improved OS

CI = confidence interval; N = number of studies; NSCLC = non-small cell lung cancer; OS = overall survival
Source: Table constructed during the commentary

⁴² Klarenbeek, SE, et al 2023, 'Impact of time-to-treatment on survival for advanced non-small cell lung cancer patients in the Netherlands: a nationwide observational cohort study', *Thorax*, vol. 78, no. 5, May, pp. 467-475 10.1136/thoraxjnl-2021-218059.

⁴³ Hoang, T, et al 2020, 'Comparative Efficacy of Targeted Therapies in Patients with Non-Small Cell Lung Cancer: A Network Meta-Analysis of Clinical Trials', *J Clin Med*, vol. 9, no. 4, Apr 9, 10.3390/jcm9041063.

⁴⁴ NCCN 2025, 'National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.4.2025', https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Effect of time to treatment on health outcomes

Two studies examined the relationship between time to treatment initiation (TTI) and health outcomes in patients with advanced NSCLC. Scott et al. (2024)⁴¹ found that patients who began targeted therapy immediately had significantly better OS compared to those who initially received non-targeted therapy while awaiting molecular test results. Specifically, patients who started on targeted therapy had a median OS of 28.8 months, whereas those who switched to targeted therapy after a delay (within 35 days) had a median OS of 21.7 months. This suggests that timely initiation of appropriate therapy is clinically beneficial.

In contrast, Klarenbeek et al. (2023)⁴² did not observe a statistically significant association between TTI and health outcomes in patients receiving targeted therapy. However, paradoxical findings were reported for patients on chemotherapy or immunotherapy, where longer TTI was associated with reduced mortality risk—likely reflecting a “sicker, quicker” effect, where more acutely ill patients received treatment sooner. Due to uncontrolled confounding and differences in healthcare settings, the applicability of Klarenbeek’s findings to the Australian context is limited. Overall, the evidence supports the clinical value of faster TTI for targeted therapy, though its impact may be influenced by other patient and system-level factors (GRADE: ⊕⊖⊖⊖).

Clinical claim

The clinical claim made for population 2 was that *“in patients newly clinically diagnosed with lung cancer and histologically or cytologically confirmed NSCLC whose initial tissue biopsy was insufficient for tissue-based genetic testing or failed tissue-based genetic testing, ctDNA testing is superior in effectiveness and safety compared to current standard of care (tissue-based genetic testing where tissue re-biopsy was feasible, and no molecular testing where tissue re-biopsy was not feasible)”*.

Direct evidence showed that in direct comparisons, NGS via ctDNA testing is non-inferior to tissue-based testing in terms of its impact on health outcomes among patients with NSCLC. It should be noted that these results are very uncertain (assessed as very low certainty of evidence) due to the small, heterogeneous population cohorts and uncertainty regarding the applicability of the comparator arm. No direct evidence on targeted treatment after ctDNA testing in NSCLC compared to standard of care (no molecular testing and standard treatment) was presented in the ADAR.

The evidence demonstrated that compared to tissue NGS, ctDNA testing NGS has a high specificity and a moderate sensitivity for detecting actionable alterations in patients with NSCLC. A limitation with the use of ctDNA testing NGS is the lower positive percent agreement (PPA) and false negative rates.

Evidence was provided showing that a proportion of patients with actionable variants detected with ctDNA testing have a change in treatment (to targeted therapy), and that patients who receive targeted therapies have superior health outcomes compared to those who receive non-targeted therapy.

The commentary considered that, compared to no molecular testing, use of ctDNA testing would be superior in effectiveness and non-inferior in safety. However, compared to a rebiopsy and testing of tumour tissue, ctDNA testing would have superior safety, but potentially inferior effectiveness, due to ctDNA testing missing cases that would have tested positive on tumour tissue, but are negative on ctDNA testing (resulting in patients missing out on targeted treatments). Some additional cases would potentially be eligible for targeted treatment due to being positive on ctDNA testing (when they would have been negative on tumour tissue), and the magnitude of benefit of the targeted treatments in this population is unknown.

Population 3

Direct from test to health outcomes evidence

The ADAR identified two studies with test to health outcomes evidence in patients who had NSCLC and had received either a first-line *EGFR*-TKI (Papadimitrakoulou et al. 2020)⁴⁵ or an *ALK*-TKI (Shaw et al. 2019)⁴⁶.

Papadimitrakoulou et al. (2020) compared treatment response to osimertinib and platinum chemotherapy in patients who were positive for an *EGFR* T790M variant in either tumour tissue or based on ctDNA testing, and retrospectively analysed the results based on whether patients were positive or negative for T790M variants based on ctDNA testing (Table 21). Patients identified through either means had better PFS and ORR if randomised to osimertinib rather than platinum chemotherapy, but the authors reported that being positive on ctDNA testing was associated with a higher disease burden (poor prognosis), with worse outcomes regardless of which treatment was received. The ADAR concluded that this demonstrates that health outcomes of ctDNA testing and targeted treatment results in superior health outcomes to receiving non-targeted treatment, which would be the default in the absence of molecular testing.

Table 21 Response to treatment according to plasma T790M status

Treatment	ctDNA-positive for T790M (tissue-positive or negative or unknown for T790M) (N=190)	ctDNA negative for T790M/tissue-positive for T790M (N=101)
Osimertinib	PFS: 8.2 months; 95% CI: 6.8, 9.7 months ORR: 68% (93 of 137); 95% CI: 59, 76%	PFS: 12.5 months; 95% CI: 10.9 months to not calculable ORR: 78% (56 of 72); 95% CI: 66, 87%
Platinum-pemetrexed	PFS: 4.2 months; 95% CI: 4.1, 5.6 months ORR: 40% (21 of 53); 95% CI: 27, 54%	PFS: 5.6 months; 95% CI: 2.8, 6.7 months ORR: 17% (5 of 29); 95% CI: 6, 36%
Hazard ratio (osimertinib vs platinum-pemetrexed)	HR: 0.40; 95% CI: 0.28, 0.58	HR: 0.27; 95% CI: 0.15, 0.49

CI = confidence interval; HR = hazard ratio; N = number of studies; ORR = objective response rate; PFS = progression-free survival; T790M = Thr790Met, methionine for threonine at amino acid position 790
Source: Table 51, p126 MSAC 1798 ADAR

Shaw et al. (2019) reported on a trial of lorlatinib in patients who had been diagnosed with *ALK*-positive NSCLC and progressed on prior second-generation *ALK* inhibitors (Table 22). After tumour progression, patients had either tumour tissue or a ctDNA testing tested for *ALK* status (although archival tumour tissue status was accepted if a rebiopsy was considered a safety risk). Patients who still had *ALK* variants detected after progression responded to lorlatinib better than those without *ALK* variants after progression. Patients positive on ctDNA testing had worse health outcomes than those positive on tumour tissue (median PFS 7.3 months vs 11 months). Without a comparison treatment group, it is difficult to determine whether the poorer results are due to prognostic factors (e.g. as presence of ctDNA detectable in blood has been reported to be a

⁴⁵ Papadimitrakoulou, VA, et al 2020, 'Epidermal growth factor receptor mutation analysis in tissue and plasma from the AURA3 trial: Osimertinib versus platinum-pemetrexed for T790M mutation-positive advanced non-small cell lung cancer', *Cancer*, vol. 126, no. 2, Jan 15, pp. 373-380 10.1002/cncr.32503.

⁴⁶ Shaw, AT, et al 2019, 'ALK Resistance Mutations and Efficacy of Lorlatinib in Advanced Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer', *J Clin Oncol*, vol. 37, no. 16, Jun 1, pp. 1370-1379 10.1200/JCO.18.02236.

prognostic marker⁴⁷), or differential response to treatment. The commentary suggested that if patients are found to have an *ALK* gene rearrangement on their primary tissue biopsy sample, they would be eligible for lorlatinib following progression on crizotinib or other *ALK*-TKIs, without further testing being required after progression (as the listing is silent on line of therapy or timing of testing). In this instance, although ctDNA testing may provide prognostic information, it would not necessarily be used to alter management.

Table 22 Response to lorlatinib based on *ALK* mutation status by plasma or tissue testing

Test outcome	Plasma status for <i>ALK</i>	Tissue status for <i>ALK</i>
Positive (n=34 plasma N=76 tissue)	PFS: 7.3 months; 95% CI: 4.1, 13.1 months ORR: 62%; 95% CI: 44%, 78%	PFS: 11 months; 95% CI 6.9 months to NR ORR: 69%; 95% CI: 49%, 85%
Negative (n=94 plasma)	PFS: 5.5 months; 95% CI: 4.1, 8.2 months ORR: 32%; 95% CI: 23%, 42%	PFS: 5.4 months; 95% CI: 3.9, 6.9 months ORR: 27%; 95% CI: 18%, 38%
Hazard ratio (positive vs negative)	HR: 0.81; 95% CI: 0.50, 1.31	HR: 0.47; 95% CI 0.27, 0.83

ALK = ALK receptor tyrosine kinase; CI = confidence interval; HR = hazard ratio; n = number of patients; N = number of studies; NR = not reported; ORR = objective response rate; PFS = progression-free survival

Source: Table 52, p127, MSAC 1798 ADAR

Linked evidence – Test performance

Test performance

The ADAR did not provide an assessment of testing concordance for population 3, claiming that this had been evaluated in population 2. However, the concordance of testing may differ between populations. Lin et al. (2021) reported a trend toward reduced accuracy of ctDNA testing in the post-treatment setting. The ADAR therefore extracted concordance data where possible.

The ADAR presented three studies^{49,50,48} that reported concordance between ctDNA testing against tumour tissue testing, in patients who had undergone both, after progression while on targeted treatment. The positive percent agreement and negative percent agreement showed highly variable concordance (PPA: 41.7% - 68.4%; NPA: 16.7% - 80.0%). Lin et al. (2021)⁴⁹ reported that tissue-based testing was more accurate and sensitive at detecting clinically relevant variants than NGS of ctDNA testing (p=0.001).

The most applicable study was by Park et al. (2021)⁵⁰, which included a cohort of patients who had progressed on a TKI (not specific to one type). Although the yield of ctDNA testing and tumour tissue testing was similar (18 vs 19 patients with actionable variants), the overall concordance ((true positives + true negatives)/total) was only 56%. This means that both tests detected patients with variants that the other method had missed.

⁴⁷ Yang, Y, et al 2022, 'The clinical utility of dynamic ctDNA monitoring in inoperable localized NSCLC patients', *Mol Cancer*, vol. 21, no. 1, May 19, p. 117 10.1186/s12943-022-01590-0.

⁴⁸ Hou, T, Zeng, et al 2022, 'Performance of different methods for detecting T790M mutation in the plasma of patients with advanced NSCLC after developing resistance to first-generation EGFR-TKIs in a real-world clinical setting', *Mol Clin Oncol*, vol. 16, no. 4, Apr, p. 88. 10.3892/mco.2022.2521

⁴⁹ Lin, LH, et al 2021, 'Comparison of solid tissue sequencing and liquid biopsy accuracy in identification of clinically relevant gene mutations and rearrangements in lung adenocarcinomas', *Mod Pathol*, vol. 34, no. 12, Dec, pp. 2168-2174 10.1038/s41379-021-00880-0.

⁵⁰ Park, S, et al 2021, 'High concordance of actionable genomic alterations identified between circulating tumor DNA-based and tissue-based next-generation sequencing testing in advanced non-small cell lung cancer: The Korean Lung Liquid Versus Invasive Biopsy Program', *Cancer*, vol. 127, no. 16, Aug 15, pp. 3019-3028 10.1002/cncr.33571.

Yield of actionable alterations

Four studies were included in the ADAR on the yield of actionable alterations. The commentary added two more (one identified from an independent search, and one that was already included in the ADAR for other outcomes) (

Table 23). Only two of the studies compared the yield between ctDNA testing and tumour tissue testing and reported that testing on tumour tissue was more sensitive than ctDNA testing. Park et. (2021) reported similar yields between testing methods, whereas Lin et al. (2021) reported significantly more actionable variants were identified from tissue testing than ctDNA testing.

The most applicable yield study was by Sabari et al. (2019), which reported on ctDNA testing after progression on targeted therapy in patients from either Australia or the United States. In this study, the proportion of patients with a clinically actionable variant (applicable to Australia) was only 33.3%, which was similar to a study by Lin et al. (2021) from the United States, but significantly lower than reported by Park et al. (2021), who reported that in Korea, 72% had actionable variants. As acknowledged by the ADAR, Asian populations have a higher proportion of patients with targetable alterations than non-Asians.¹³

Table 23 Yield of actionable variants by ctDNA testing and tumour tissue testing

Study	N	CtDNA testing yield	Tissue testing yield
Park 2021	25 patients with progression on TKI	Actionable: 18/25 (72%)	Actionable: 19/25 (76%)
Laufer-Geva 2018	28 patients with progression on EGFR-TKI	Actionable: (assuming EGFR sensitising not relevant if have progressed on EGFR-TKI): 50.1%	NR
Lin 2021	29 patients who had progression on (majority targeted) treatment	Clinically relevant (not necessarily actionable): 11/29 (37.9%)	Clinically relevant (not necessarily actionable): 24/29 (82.7%)
Mack 2020 ⁵¹	447 with progression on any EGFR-TKI (48 third generation EGFR-TKI)	Actionable (total): 277/447 (61.9%)	NR
Mondaca 2021 ⁵²	7 with disease progression on ALK targeted therapy Potential overlap with Sabari 2019	Actionable: 4/7 (57.1%)	NR 3 cases where ALK fusion was detected by tissue NGS but not on ctDNA (when tested for resistance mechanism)
Sabari 2019	57 with progression on targeted therapy	Actionable (total): 22/57 (38.6%) Total actionable in Australia currently: 19/57 (33.3%)	NR

ALK = ALK receptor tyrosine kinase; ctDNA = circulating tumour deoxyribonucleic acid; EGFR = epidermal growth factor receptor; N = number of studies; NGS = next-generation sequencing; NR = not reported; TKI = tyrosine kinase inhibitor

Source: amended from Table 54, p130 MSAC 1798 ADAR

⁵¹ Mack, PC, et al 2020, 'Spectrum of driver mutations and clinical impact of circulating tumor DNA analysis in non-small cell lung cancer: Analysis of over 8000 cases', *Cancer*, vol. 126, no. 14, Jul 15, pp. 3219-3228 10.1002/cncr.32876.

⁵² Mondaca, Set al 2021, 'Clinical utility of next-generation sequencing-based ctDNA testing for common and novel ALK fusions', *Lung Cancer*, vol. 159, Sep, pp. 66-73 10.1016/j.lungcan.2021.06.018.

Linked evidence – Change in management

Tissue rebiopsy adequacy

In patients with a recurrence of disease, ctDNA testing was proposed as an alternative to rebiopsy in those who could not tolerate a rebiopsy, or where rebiopsy had failed to retrieve sufficient tissue for genetic testing. Therefore, the proportion of patients who cannot tolerate a rebiopsy, or those in whom a rebiopsy provided insufficient tissue, was relevant. The ADAR presented two studies and one systematic review and meta-analysis that included this outcome. The meta-analysis was considered by the commentary to be the most informative, capturing the most information. The meta-analysis by Nam et al. (2021) included 13 studies, with a total of 1,517 patients with NSCLC who underwent rebiopsies. The pooled tissue adequacy rate for rebiopsy was 87% (95% CI 84%, 90%) (overall adequacy rate for initial biopsy and rebiopsy 89%, 95%CI 86% to 93%) (Figure 2).

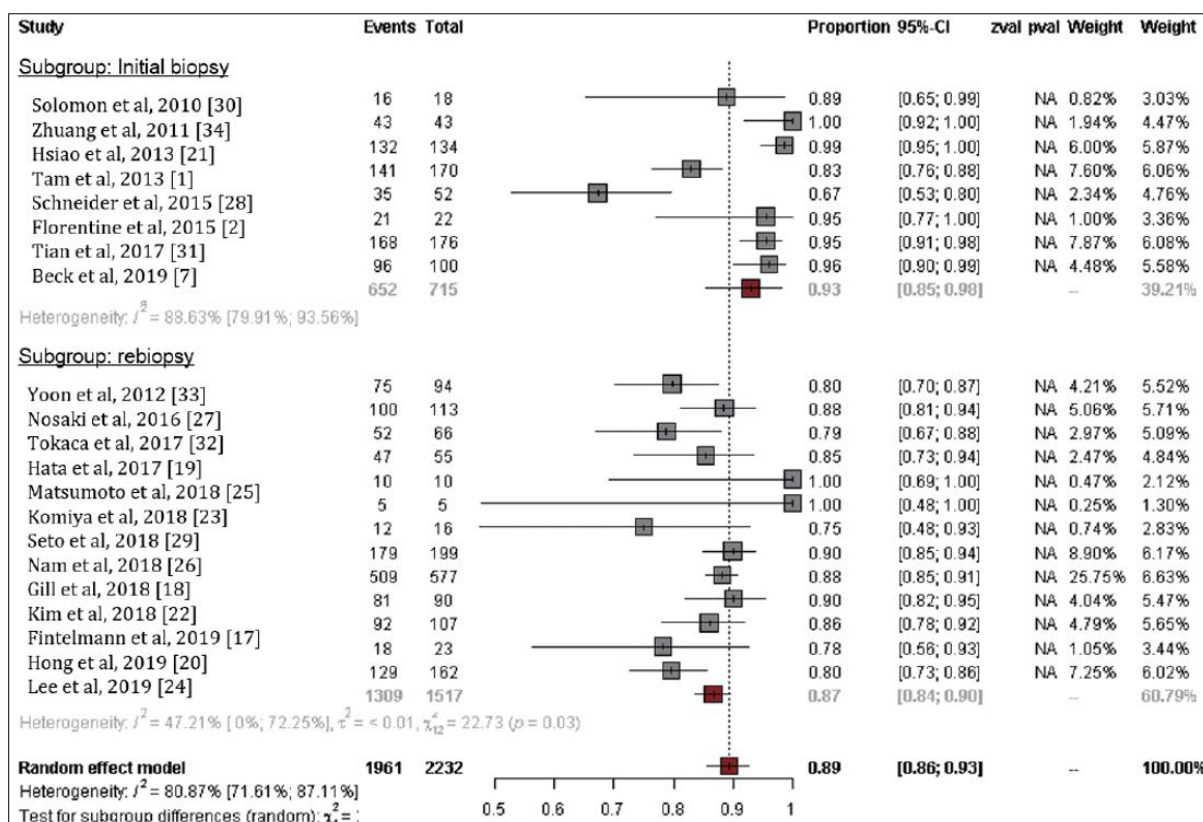


Figure 2 Tissue adequacy rate of percutaneous transthoracic needle biopsy for molecular analysis in NSCLC

Source: Nam 2021 Figure 2B p2087, Permission to reproduce under Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>)

Treatments received based on ctDNA testing

The ADAR reported on three studies that described the targeted treatments that patients received, after they were identified with actionable variants on ctDNA testing. The commentary identified one additional study not identified by the ADAR (Laufer-Geva et al. 2018) (

Table 24). Three out of four studies reported only on the impact of ctDNA testing after patients had progression on an EGFR-TKI (in which case a T790M variant frequently resulted in the initiation of osimertinib). The applicability of this to the current Australian healthcare setting is limited, as osimertinib has become the preferred first-line treatment for patients with sensitising EGFR variants, and is only allowed to be given as a single line of treatment. The remaining study (Sabari et al. 2019) was more relevant to the Australian setting. This study included patients

from Australia, and described a wider range of impacts that broad based testing may have, after progression on first-line targeted therapy. In this study, a third of those who were tested with ctDNA testing had a variant identified, that allowed them to have a subsequent targeted treatment that is available on the PBS (or recommended to be by PBAC). Although this trial did not restrict use of ctDNA testing to those who could not tolerate a tissue biopsy, the results are assumed to be applicable to those in whom a biopsy is infeasible.

Table 24 Treatments received subsequent to ctDNA testing genetic testing

Study	Population	Treatment received
Sabari 2019	57/210 patients (27.1%) with NSCLC who had known driver alterations and were categorised as resistance mechanism unknown with disease progression at the time of plasma testing.	22 (38.5%) patients were identified with relevant alterations out of 57 patients with progression on targeted therapy. All patients received ctDNA-directed therapy: 22/22 (100%). 19/57 (33.3%) had variants relevant to targeted therapies available currently or in the near future in Australia (shown in bold) (and received ctDNA-direct therapy) EGFR exon 20 T790M was identified in 3 patients who were then matched to osimertinib (3/3 = 100%). MET amplification was detected in one patient (who was started on a clinical trial protocol of osimertinib plus MET inhibitor savolitinib (1/1=100%). ALK rearrangements were identified in 7 patients, 3 of whom were matched to crizotinib and 4 were matched to alectinib in the first-line setting (7/7=100%). ERBB2 mutation was identified in one patient who enrolled in a clinical trial with ado-trastuzumab emtansine (NCT02675829) (100%). BRAF L579Q was identified in one patient who enrolled on a phase I trial of ulixertinib (ERK inhibitor) (NCT01781429) (100%). BRAF V600E was identified in 2 patients who were both matched to dabrafenib and trametinib (100%). MET exon14 skipping alterations were identified in 6 patients; all were matched to targeted therapy with crizotinib. (100%). RET fusion was identified in one patient, who was matched to cabozantinib (100%).
Tran 2021	14 of 100 patients had a second ctDNA test at disease progression.	8/14 (57.1%) had alteration in treatment A change in therapy from erlotinib to osimertinib occurred in 6 with identification of EGFR exon 20 T790M at the time of disease progression 2 additional patients had dual EGFR L858R plus T790M and switched from erlotinib to osimertinib. Remaining patients had no changes in variants identified (no changes in treatment mentioned).
Lin 2024	26 patients who progressed on EGFR-TKI and had inadequate tissue for NGS after rebiopsy, with ctDNA NGS results only	5/26 had EGFR T790M variant identified in ctDNA testing, and 4/26 (15.3%) received osimertinib.
Laufer-Geva 2018	Advanced NSCLC patients who had progression on EGFR-TKI	9/28 (32%) had treatment influenced by ctDNA testing results

ALK = ALK receptor tyrosine kinase; BRAF = B-Raf proto-oncogene, serine/threonine kinase; ctDNA = circulating tumour deoxyribonucleic acid; EGFR = epidermal growth factor receptor; ERBB2 = erb-b2 receptor tyrosine kinase 2; MET = MET proto-oncogene, receptor tyrosine kinase; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; RET = ret proto-oncogene; T790M = Thr790Met, methionine for threonine at amino acid position 790; TKI = tyrosine kinase inhibitor

Source: Table 57, pp134-135 MSAC 1798 ADAR

Linked evidence – Impact of change in management on health outcomes

The article by Sabari et al. (2019) also reported on whether patients responded to the ctDNA-biopsy-directed treatment or not (Table 25). All patients were classified as having a partial response to their second-line targeted treatment. The ADAR suggested that a partial response may be more likely than a complete response in patients with more advanced disease. In the absence of data on what the health outcomes of these patients would be on non-targeted therapy, the size of benefit of patients being able to access a second targeted therapy is unknown (GRADE: ⊕⊕⊖⊖).

Table 25 Response to targeted treatments in patients identified with actionable variants post-progression

Study	Population	Health outcomes
Sabari 2019	N=22 patients with resistance to targeted therapy, who had a clinically actionable variant identified on ctDNA testing post-progression and had another line of targeted treatment	<p><i>EGFR</i> exon 19 with <i>MET</i> amplification (n=1) led to clinical trial: osimertinib + savolitinib (no health outcomes available)</p> <p><i>MET</i>ex14sk (n=6) led to crizotinib 2/2 with health outcomes partial response, other 4 not available</p> <p><i>EGFR</i> T790M (n=3) led to osimertinib: 3/3 PR</p> <p><i>EML4-ALK</i> (n=3) led to crizotinib: 3/3 PR</p> <p><i>EML4-ALK</i> (n=3) led to alectinib 3/3 PR</p> <p><i>ALK</i> (n=1) led to alectinib 1/1 PR</p> <p><i>BRAF</i> V600E (n=2) led to clinical trial: dabrafenib + trametinib 2/2 PR</p> <p><i>BRAF</i> L597Q (n=1) led to clinical trial ulixertinib 1/1 PR</p> <p><i>ERBB2</i> (n=1) led to clinical trial trastuzumab 1/1 PR</p> <p><i>RET</i> arrangement (n=1) led to cabozatinib 1/1 PR</p>

ALK = ALK receptor tyrosine kinase; BRAF = B-Raf proto-oncogene, serine/threonine kinase; EGFR = epidermal growth factor receptor; ERBB2 = erb-b2 receptor tyrosine kinase 2; MET = MET proto-oncogene, receptor tyrosine kinase; METex14sk = MET proto-oncogene, receptor tyrosine kinase exon 14 skipping; N = number of studies; n = number of patients; RET = ret proto-oncogene; T790M = Thr790Met, methionine for threonine at amino acid position 790
 Source: Table 61, p138 MSAC 1798 ADAR

Clinical claim

The clinical claim made for patients with recurrence or progression of NSCLC disease after first-line (1L) targeted therapy, was that ctDNA testing is superior in effectiveness and non-inferior in safety compared to current standard of care (no molecular testing if post progression tissue biopsy is not feasible or biopsy and/or tissue test fails).

It is unknown what proportion of patients would be considered unsuitable for tissue biopsy. However, evidence included in the ADAR suggested that, of those patients who are considered able to tolerate a rebiopsy, 87% have sufficient tumour tissue retrieved for molecular testing to occur. The remaining 13% would be the target population. The evidence suggested that for population 3, ctDNA testing resulted in smaller yields of clinically actionable variants than testing of tumour tissue, and there was a trend towards poorer concordance between ctDNA testing results and tumour tissue results in patients tested post-progression than in treatment naïve patients (population 2). However, if the comparator is no testing, then any additional patients with clinically actionable variants identified would be more than if molecular testing were not performed. A single study provided good evidence that post-progression testing may detect actionable variants broader than just *EGFR* T790M, and the identification of these variants results in second-line targeted treatments being used, which patients partially respond to. The evidence is highly uncertain that this is superior to no testing and use of non-targeted therapy, as there were no studies comparing second-line targeted therapy versus standard of care treatments for those without actionable variants after failure of first-line targeted treatments.

However, the commentary considered that it is likely that the clinical claim was met, that testing would result in superior effectiveness. Safety of testing would be considered non-inferior, due to only minor adverse events associated with venipuncture, and the different but non-inferior safety associated with targeted therapies.

No clinical claim was made regarding the comparator that PASC suggested – rebiopsy and testing of tumour tissue. The limited comparative evidence suggested that ctDNA testing was inferior to testing of tumour tissue if the number of variants tested were the same for each technique.

13. Economic evaluation

The ADAR presented a separate cost-effectiveness analysis for each of the 3 proposed populations. This was consistent with the claims of superior effectiveness and non-inferior (or superior) safety presented in the ADAR. The commentary considered that the claims of superior and non-inferior safety were reasonable where ctDNA testing was compared to no testing, however, were considered to be potentially inferior when compared to tissue biopsy, where able to be performed. As PASC suggested that ctDNA testing be used only where tissue rebiopsy was not feasible or had failed, the presentation of cost-effectiveness analyses may only be appropriate against comparators of no testing for each of the proposed populations.

For each of the analyses, the ADAR truncated the model at the time of treatment decisions. The commentary considered that while cost-utility analyses would be preferred that capture the costs and outcomes of changes in treatment due to ctDNA testing, truncation of the economic models might be reasonable where the cost-effectiveness for changes in treatment could reasonably be inferred (i.e. if the treatment effect in patients diagnosed by ctDNA testing and panel testing would be the same as in those patients with biomarkers identified from tissue biopsy and testing methods used in the trials). However, the commentary noted that this might not be a reasonable inference, due to the negative percent agreement reported for ctDNA testing ('Test performance' for population 2) which would result in additional positives following ctDNA testing that would not have been identified through tissue-based testing. As described in 'Clinical claim' for population 2, the commentary considered that the magnitude of benefit from targeted therapy in patients with these discordant positive results is unknown. Therefore, the commentary considered that it was unclear whether the cost-effectiveness for the additional patients with discordant positive results treated following ctDNA testing could reasonably be inferred.

A summary of the key components of the ADAR's economic analyses is presented in Table 26.

Table 26 Key components of the economic evaluations presented in the ADAR

Component	Population 1	Population 2	Population 3
Perspective	Australian healthcare system perspective		
Population	Patients with a clinical diagnosis of lung cancer in whom tissue biopsy is not available or feasible.	Newly diagnosed patients with NSCLC (any stage) whose initial biopsy was insufficient for or had failed testing.	Patients with NSCLC who have progressed on targeted therapy and in whom tissue biopsy is not feasible or has failed.
Comparator	No testing.	No testing or tissue rebiopsy and tissue-based testing.	No testing.
Type(s) of analysis	Cost-effectiveness analysis.		
Outcomes	Patients with actionable alterations identified.	Patients with actionable alterations identified.	Patients identified with informative results.
Time horizon	Time to treatment decisions		
Computational method	Decision tree analysis		
Generation of the base case	Modelled analysis incorporating different aspects of the linked evidence		
Discount rate	Not applicable		
Software	Microsoft Excel and TreeAge Pro.		

Abbreviations: NSCLC = non-small cell lung cancer.

Source: Adapted from Table 71 of the ADAR.

Population 1

In population 1, patients with a clinical diagnosis of lung cancer in whom tissue biopsy was not available or had failed were modelled. The commentary considered that while this was consistent with the wording of the proposed item descriptors in the ADAR, as noted in 'Proposal for public funding', the proposed wording by PASC specified that patients must be suspected of having NSCLC. As noted in the 'Characteristics of the evidence base for Population 1' evidence presented in the ADAR were restricted to those patients suspected of NSCLC.

In this population, identification of actionable alterations was assumed to enable patients to receive targeted therapies instead of chemotherapy options which do not require histological confirmation of disease. The commentary considered that this assumption was dependent on whether patients could be eligible for NSCLC-targeted treatments without histopathological confirmation of NSCLC.

The key inputs used in the economic evaluation for population 1 are presented in Table 27.

Table 27 Summary of the model inputs (population 1)

Input	Value applied (source)	Comment
Success of ctDNA testing	100% (Aggarwal et al. 2019)	The ADAR assumed that on ctDNA testing test failure, repeat testing would occur on another aliquot of blood. The commentary noted that reasons for test failure would likely require a new sample to be obtained (and may require a professional attendance to request the additional blood draw). However, due to the high success rate (98–100%), the impact of this is minor.
Yield of actionable alterations		
• Base case ^a	22.0% (Garcia-Pardo et al. 2023) ²¹	The commentary noted that ADAR did not consider the applicability of the yield estimate to the proposed setting or consider alternate sources identified in the clinical evaluation.
• Scenario analyses	+ <i>BRAF</i> : 22.6% + <i>BRAF, ERBB2 (HER2)</i> : 24.5% + <i>BRAF, ERBB2 (HER2), KRAS</i> : 34.3% (assuming the proportionate increase in yield for the relevant scenarios as observed for ctDNA testing in population 2)	While the commentary noted minor issues regarding the yield estimate applied in the base case (above), due to the proportionate increase in yield applied, the relative impact on the ICER across the scenario analyses tested would be similar.
Proportion of patients with advanced disease at diagnosis, or who progress	91.4% (tissue-based testing yield for population 2 adjusted for patients with advanced disease at diagnosis or who progress [25.6%] as a proportion of total yield [28.0%], Table 34)	The commentary considered that it may not be appropriate to use tissue-based testing estimates of yield to derive this proportion. However, using ctDNA-based estimates had a minor impact on this estimate (91.6%)
ctDNA testing test cost	\$3,000 (proposed fee).	While consistent with the proposed fee for ctDNA testing, the commentary considered that given the comparison to no testing, the cost of an additional consultation to review results may also apply.

ALK = ALK receptor tyrosine kinase; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; *EGFR* = epidermal growth factor receptor; *ERBB2 (HER2)* = erb-b2 receptor tyrosine kinase 2 (previously known as *HER2*); *ICER* = incremental cost-effectiveness ratio; *KRAS* = *KRAS* proto-oncogene, GTPase; *METex14sk* = *MET* proto-oncogene, receptor tyrosine kinase exon 14 skipping; *NTRK* = neurotrophic receptor tyrosine kinase; *RET* = ret proto-oncogene; *ROS1* = *ROS* proto-oncogene 1, receptor tyrosine kinase.

Note: Revised estimates in *italics* text were applied for *BRAF* and *KRAS* yield to reflect the subset of variants near-market therapies target (i.e. *BRAF* V600E or *KRAS* G12C).

^a Includes variants in the following genes: *EGFR*, *ALK*, *ROS1*, *METex14sk*, *NTRK* and *RET*

Source: Adapted from Table 74 of the ADAR.

The results of the economic evaluation for population 1 are presented in Table 28.

Table 28 Results of the economic evaluation (population 1)

	ctDNA testing	SOC	Increment
Cost	\$3,000.00	\$0.00	\$3,000.00
Actionable alterations identified	20.1% ^a	0.0%	20.1%
Incremental cost per additional actionable alteration identified			\$14,915

SOC = standard of care

^a Calculated from the success of ctDNA testing (100.0%) × yield of actionable variants (22.0%) × proportion of patients with advanced disease (91.4%) (see Table 27).

Source: Adapted from Table 85 and Table 86 of the ADAR.

The key driver of the analysis was the yield of actionable alterations. As described in Table 27, this was based on the number of patients found with relevant variants by ctDNA testing in a

cohort of Canadian patients with suspected NSCLC tested (Garcia-Pardo et al. 2023)²¹ (22.0%) ('Yield of actionable alterations' for population 1). The ADAR did not consider the applicability of the yield estimate applied to the proposed setting or justify the use of this source in preference to alternate sources identified in the clinical evaluation. The ADAR adjusted the yield to account for patients diagnosed at early-stage disease who would not progress to advanced disease, derived from estimates from population 2 (91.4%)⁵³. The resulting yield applied was 20.1%.

The commentary considered an alternate approach that adjusts the yield of actionable variants following ctDNA testing in population 2 by the proportion of patients tested who have NSCLC. Based on the evidence presented in the ADAR ('Yield of actionable alterations' for population 1), the pre-test probability of NSCLC in those suspected was 69.0%; applying this to the yield of actionable variants following ctDNA testing in population 2 (23.2%, Table 34) would result in an overall yield of 16.0%. The commentary considered that this may better reflect yield in the proposed population if yield in those suspected found to have NSCLC is similar to those patients able to receive histopathological confirmation of disease.

The results of key scenario and univariate sensitivity analyses for population 1 are summarised in Table 29.

Table 29 Scenario and sensitivity analyses (population 1)

Analyses	Incremental cost	Incremental actionable alterations ^a	ICER per additional actionable alteration	% change in ICER
Base case	\$3,000	20.1%	\$14,915	-
<i>Yield, base case: 20.1%</i>				
<i>16.0%, based on yield in previously untreated patients expected in practice (23.2%, see Table 34), adjusted for the proportion of patients tested who have NSCLC (69.0%)</i>	\$3,000	16.0%	\$18,750	26%
Scenario analyses (base case: testing unrestricted by disease stage, actionable alterations include <i>EGFR</i> , <i>ALK</i> , <i>ROS1</i> , <i>MET</i> 14sk, <i>NTRK</i> and <i>RET</i>)				
Restricting testing to advanced disease	\$3,000	22.0%	\$13,636	-9%
<i>Expanding actionable alterations to include BRAF</i>	\$3,000	20.7%	\$14,513	-3%
<i>Expanding actionable alterations to include ERBB2 (HER2) and BRAF</i>	\$3,000	22.4%	\$13,381	-10%
<i>Expanding actionable alterations to include ERBB2 (HER2), BRAF and KRAS</i>	\$3,000	31.4%	\$9,566	-36%
Applicant's pre-MSAC response: Updated base case (Restricting testing to advanced disease, ctDNA testing cost \$3,000)				
Updated base case	\$3,000	22.0%	\$13,636.36	0%
CtDNA testing cost \$2,500	\$2,500	22.0%	\$11,363.64	-17%
CtDNA testing cost \$2,200	\$2,200	22.0%	\$10,000.00	-27%

ALK = ALK receptor tyrosine kinase; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; *EGFR* = epidermal growth factor receptor; *ERBB2 (HER2)* = erb-b2 receptor tyrosine kinase 2 (previously known as *HER2*); *ICER* = incremental cost-effectiveness ratio; *KRAS* = KRAS proto-oncogene, GTPase; *MET*14sk = MET proto-oncogene, receptor tyrosine kinase exon 14 skipping; NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic receptor tyrosine kinase; *RET* = ret proto-oncogene; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase

Note: Analyses in *italics* text were conducted during the evaluation. Revised estimates for *BRAF* and *KRAS* yield were applied to reflect the subset of variants near-market therapies target (i.e. *BRAF* V600E or *KRAS* G12C).

⁵³ adjusted [25.6%] as a proportion of total [28.0%] yield following tissue testing reported in population 2.

^a Unless otherwise described, calculated from the success of ctDNA testing × yield of actionable variants × proportion of patients with advanced disease
 Source: Adapted from Table 88 of the ADAR.

Population 2

The population the ADAR modelled included patients of any disease stage whose initial biopsy was insufficient or had failed testing, and so the comparator modelled was tissue biopsy and testing in those patients where feasible, and no testing where tissue biopsy was not feasible. The commentary considered that this was not consistent with PASC advice that ctDNA testing be restricted to patients with locally metastatic and advanced disease only where tissue biopsy is not feasible or has failed. Results were presented in the commentary to reflect the PASC-preferred base case.

As ctDNA testing may miss patients who would otherwise have been detected through tissue-based testing, the ADAR base case assumed that tissue biopsy would follow negative ctDNA testing results, in all patients where this was able to be performed. The commentary considered that this assumption would not apply in the PASC-preferred base case.

The key inputs used in the economic evaluation for population 2 are presented in Table 30.

Table 30 Summary of the model inputs (population 2)

Input	Value applied (source)	Comment
Rate of re-biopsy (upfront or after negative ctDNA testing result)	80% (MSAC Application 1721)	The commentary noted that the 80% rate applied in MSAC Application 1721 referred to the success rate of testing following rebiopsy, rather than the proportion able to undergo a rebiopsy (assumed to be 100%).
Success of tissue biopsy and testing	76.4% (Fielding et al. 2024) ⁵⁴ .	The commentary noted that this study was not applicable for the success rate of tissue testing following rebiopsy, as estimates reported reflected the proportion of patients who had insufficient tissue from their initial biopsy or did not receive testing. The estimate applied however was similar to the weighted average tissue rebiopsy failure rate in the included studies (73.7%, 'Test success rate' for population 2).
Success of ctDNA testing	100% (Aggarwal et al. 2019)	As described in Table 27, reasons for test failure may require a new sample (and professional attendance) to be obtained. However, the impact of this is minor.
Yield of actionable alterations		
<ul style="list-style-type: none"> • Base case ^a 	Tissue-based testing: 28.0% ^b ctDNA-based testing: 25.3% (tissue-based testing yield adjusted using gene-specific concordance estimates derived in the clinical evaluation, Table 34).	The ADAR did not consider that the yield of variants by tissue-based testing varies based on the method used (see MSAC Application 1721). As concordance data were based on comparisons to tissue NGS, the commentary considered that expected yield from tissue-based testing should also reflect yield using panel-based methods. While yield estimates applied were generally similar, the yield of <i>ALK</i> rearrangements may have been underestimated.

⁵⁴ Fielding D, et al 2024. Evaluation of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA) Samples from Advanced Non-Small Cell Lung Cancer for Whole Genome, Whole Exome and Comprehensive Panel Sequencing. *Cancers (Basel)* 16(4).

Input	Value applied (source)	Comment
• Scenario analyses	<i>ERBB2 (HER2)</i> : 2.3% (Tan and Tan 2022) ¹³ <i>BRAF</i> : 3.0% (Luk et al. 2015) ⁵⁵ <i>KRAS</i> : 25.0% (MSAC Application 1669) ⁵⁶	The ADAR did not consider that near market therapies targeting <i>BRAF</i> and <i>KRAS</i> would apply to a proportion of patients (those with <i>BRAF</i> V600E or <i>KRAS</i> G12C variants, respectively).
Proportion of patients with advanced disease at diagnosis, or who progress	75.9% (MSAC Application 1721)	The ADAR has not considered the impact of the recently implemented lung cancer screening program on the proportion of patients diagnosed with or who progress to advanced disease. The commentary considered that the proportion of patients diagnosed with early-stage disease would substantially increase.
CtDNA testing test cost	\$3,000 (proposed fee)	As described in Table 27, in the proportion of patients who would not otherwise have received tissue rebiopsy and testing, the cost of an additional consultation to review results may also apply.
Tissue rebiopsy	\$11,408 (price weights for AR-DRG E42 ^c multiplied by the NEP (2025–26) ⁵⁷ , assuming a 14% complication rate [MSAC Application 1161 and MSAC Application 1721] ⁵⁸ , and 100% inpatient).	The commentary considered that the approach used to estimate the cost of rebiopsy was not consistent with the MSAC Guidelines, which prefer costs directly applied from the latest NHCDC Cost Report. The preferred approach was also noted to account for the reduced cost associated with same-day admissions.
Tissue-based testing	\$1,201.27 based on the schedule fees and MBS statistics for items 73437, 73438 and 73439 (November 2023–June 2024) (89% combined panel, 9% DNA panel only, 2% DNA then RNA panel)	The commentary considered that while MBS item statistics reflected only the first 7 months of use, using complete 2024 calendar year data had only a minor impact on the distribution and cost of small panels used.

ALK = ALK receptor tyrosine kinase; AR-DRG = Australian Refined-Diagnosis Related Group; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; *EGFR* = epidermal growth factor receptor; *ERBB2 (HER2)* = erb-b2 receptor tyrosine kinase 2 (previously known as *HER2*); *KRAS* = KRAS proto-oncogene, GTPase; *MET*ex14sk = MET proto-oncogene, receptor tyrosine kinase exon 14 skipping; NEP = National Efficient Price; NGS = next generation sequencing; NHCDC = National Hospital Cost Data Collection; *NTRK* = neurotrophic receptor tyrosine kinase; *RET* = ret proto-oncogene; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase.

^a Includes variants in the following genes: *EGFR*, *ALK*, *ROS1*, *MET*ex14sk, *NTRK* and *RET*

^b Yield of *EGFR*: 17.9% (Erlotinib and gefitinib DUSC Report, February 2017)⁵⁹; *ALK*: 3.0% (MSAC Application 1250.1)⁶⁰; *ROS1*: 1.6% (MSAC Application 1454)⁶¹; *MET*ex14: 3.6% (Tepotinib PSD, November 2021 PBAC meeting)⁶²; *NTRK*: 0.23% (Tan and Tan 2022)¹³; and *RET*: 1.7% (Tan and Tan 2022)¹³.

^c The price weight for a complicated biopsy was weighted by the distribution of separations reported in the NHCDC Cost report 2021–22 for AR-DRG E42A and E42B.⁶³

Source: Adapted from Table 74 of the ADAR.

⁵⁵ Luk, PP, et al 2015, 'BRAF mutations in non-small cell lung cancer', *Transl Lung Cancer Res*, vol. 4, no. 2, Apr, pp. 142-148.

⁵⁶ <https://www.msac.gov.au/applications/1669>

⁵⁷ Independent Health and Aged Care Pricing Authority [IHACPA] 2025, *National Efficient Price Determination 2025–26 March 2025*, Independent Health and Aged Care Pricing Authority, Sydney, <https://www.ihacpa.gov.au/resources/national-efficient-price-determination-2025-26>.

⁵⁸ <https://www.msac.gov.au/applications/1161>

⁵⁹ <https://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/2017-02/erlotinib-and-gefitinib-non-small-cell-lung-cancer-feb-2017>

⁶⁰ <https://www.msac.gov.au/applications/1250-1>

⁶¹ <https://www.msac.gov.au/applications/1454>

⁶² <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2021-11/tepotinib-tablet-225-mg-as-hydrochloride-monohydrate>

⁶³ Independent Health and Aged Care Pricing Authority [IHACPA] 2024, *NHCDC Public Sector Report 2021-22 — March 2024*, Independent Health and Aged Care Pricing Authority, Sydney, <https://www.ihacpa.gov.au/resources/national-hospital-cost-data-collection-nhcde-public-sector-2021-22>.

The results of the ADAR base case analysis for population 2 are presented in Table 31. Results presented in the commentary consistent with the PASC-preferred scenario are presented in Table 32.

Table 31 Results of the economic evaluation (population 2, ADAR base case)

	CtDNA testing	SOC ^a	Increment
Costs			
Cost of ctDNA testing	\$3,000.00	\$0.00	\$3,000.00
Cost of tissue test	\$548.28	\$734.22	-\$185.94
Cost of re-biopsy	\$6,815.12	\$9,126.33	-\$2,311.21
Total costs	\$10,363.41	\$9,860.55	\$502.86
Outcomes			
Actionable alterations identified	26.1% ^b	15.6%	10.4%
• Identified from ctDNA testing	23.2% ^c	–	23.2%
• Identified from tissue biopsy	2.9%	15.6%	-12.8%
False negatives after ctDNA testing	6.3%	0.0%	6.3%
Discordant positive results	3.9%	0.0%	3.9%
Rate of rebiopsy	59.7%	80.0%	-20.3%
Rate of rebiopsy × rate of complications	8.4%	11.2%	-2.8%
Turnaround time (days)	10.0	42.0	-32.0
Incremental cost per additional actionable alteration identified			\$4,827

SOC = standard of care

^a Tissue rebiopsy and testing where able to be performed, and no testing where unable to be performed.

^b Includes actionable alterations following ctDNA testing and subsequent tissue rebiopsy and testing in those with noninformative ctDNA testing results.

^c Calculated from the success of ctDNA testing (100.0%) × yield of actionable variants from ctDNA testing, after adjustment for patients with advanced disease (23.2%, see Table 34).

Source: Adapted from Table 83 of the ADAR.

Table 32 Results of the economic evaluation (population 2, commentary’s PASC-preferred scenario, tissue-first restricted to advanced disease) with no possibility of a tissue re-biopsy so a no testing comparator

	CtDNA testing	SOC	Increment
Cost of ctDNA testing	\$3,000.00	\$0.00	\$3,000.00
Outcomes			
Actionable alterations identified	25.3% ^a	0.0%	25.3%
False negatives after ctDNA testing	7.3%	0.0%	7.3%
Discordant positive results	4.6%	0.0%	4.6%
Incremental cost per additional actionable alteration identified			\$11,846

SOC = standard of care

^a Calculated from the success of ctDNA testing (100.0%) × yield of actionable variants from ctDNA testing (25.3%).

Source: Constructed during the evaluation.

The key drivers of the model for population 2 are presented in Table 33. The commentary noted that for the PASC-preferred scenario, drivers related to use and cost of rebiopsy and proportion of patients with advanced disease are not relevant.

Table 33 Key drivers of the model (population 2)

Description	Method/Value	Impact ADAR base case: \$4,287/ additional actionable alteration gained
Cost of rebiopsy	\$11,408, based on price weights for AR-DRG E42 ^a multiplied by the National Efficient Price (2025–26) ⁵⁷ , assuming a 14% complication rate (MSAC Application 1161 and MSAC Application 1721) ⁵⁸ . (100% inpatient).	High, favours ctDNA testing. Assuming a cost of \$6,232 per biopsy (based on the weighted cost of AR DRG E42 reported in the NHCDC cost report 2022–23) ⁶⁴ , increased the ICER to \$14,893/actionable alteration gained. Reducing the complication rate to 10% (maintain base case cost), increased the ICER to \$5,675/actionable alteration gained. Assuming that 50% of biopsies would occur in the outpatient setting increased the ICER to \$12,123/actionable alteration gained.
Use of rebiopsy ^b	80%, based on MSAC Application 1721	High. Assuming patients are not able to undergo rebiopsy increased the ICER to \$12,932/actionable alteration gained. The ICER was dominant when assuming all patients were able to undergo rebiopsy (as per MSAC Application 1721) When use of rebiopsy was assumed to be lower following a negative ctDNA testing result, cost-savings (therefore dominant ICERs) were observed.
CtDNA testing PPA	Gene-specific meta-analyses presented in the ADAR.	High, favours ctDNA testing. Using published PPA estimates reported by Ontario Health ⁶⁵ increased the ICER to \$6,924/actionable alteration gained.
Yield	25.6% for tissue testing and 23.2% for ctDNA testing (see Table 34). Estimates were adjusted for the proportion of patients who would not develop advanced disease (below).	High, favours ctDNA testing. When a 5% patient attrition between ctDNA testing and treatment is considered, the ICER increased to \$5,517/actionable alteration gained, which further increases to \$6,438/actionable alteration gained when a 10% attrition rate is applied.
Proportion of patients with advanced disease	75.9%, based on the proportion of patients with advanced disease at diagnosis (65.5%, Mitchell et al. 2013) ⁶⁶ , or who progress to advanced disease from an earlier stage (30% of those diagnosed with early-stage disease)	Moderate, favours ctDNA testing. Assuming 47.5% of patients have advanced disease (accounting for impacts of the lung cancer screening program), increased the ICER to \$5,514/actionable alteration gained. When testing is restricted to patients with advanced disease (i.e. 100%), the ICER decreased to \$4,365/actionable alteration gained.

AR-DRG = Australian Refined-Diagnosis Related Group; ICER = incremental cost-effectiveness ratio; NHCDC = National Hospital Cost Data Collection; PPA = positive percent agreement

^a The price weight for a complicated biopsy was weighted by the distribution of separations reported in the NHCDC Cost report 2021–22 for AR-DRG E42A and E42B.⁶³

^b upfront in the comparator arm of the model, or after a negative ctDNA testing result in the intervention arm.

Source: Constructed during the evaluation.

⁶⁴ Independent Health and Aged Care Pricing Authority [IHACPA] 2025, *NHCDC Public Sector Report 2022-23 — March 2025*, Independent Health and Aged Care Pricing Authority, Sydney, <https://www.ihacpa.gov.au/resources/national-hospital-cost-data-collection-nhcdc-public-sector-2022-23>.

⁶⁵ Ontario Health 2024, Plasma-based comprehensive genomic profiling DNA assays for non-small cell lung cancer: a health technology assessment, Ont Health Technol Assess Ser [Internet].

⁶⁶ Mitchell, PL, et al 2013, 'Lung cancer in Victoria: are we making progress?', *Med J Aust*, vol. 199, no. 10, Nov 18, pp. 674-679.

The ADAR base case proposed that ctDNA testing would replace tissue biopsy where tissue rebiopsy was able to be performed and the results were most sensitive to the use and cost of rebiopsy.

The ADAR's estimated cost of rebiopsy was noted to be substantially higher than that applied in MSAC Application 1721 (\$11,408 compared to \$5,630). While the same Australian Refined Diagnosis Related Group codes were used (E42), the ADAR applied inlier price weight (1.3616) to the National Efficient Price (\$7,258), whereas MSAC Application 1721 applied costs from the National Hospital Cost Data Collection (NHCCD) Cost Report. The commentary noted that the latter approach is that preferred in the PBAC Manual of Resource Items⁶⁷ referred to in the MSAC Guidelines. This approach was also noted to account for the reduced cost associated with same-day admissions (which are associated with a lower price weight than the inlier price weight). Using the current NHCCD cost report (2022–23), the commentary estimated the average cost of biopsy (maintaining the ADAR base case complication rate) is \$6,232.

The complication rate assumed was based on MSAC consideration from 2012 (MSAC Application 1161)⁵⁸ and the commentary considered that the applicability of this estimate to the current context was not clear given likely improvements in imaging to guide biopsy over this time. The commentary noted that MSAC Application 1721 identified an alternate complication rate of 10%, based on the incidence of pneumothorax noted in MSAC Application 1660⁶⁸.

The ICER was also sensitive to the setting for rebiopsy. In the base case this was assumed to be 100% inpatient, consistent with previous analyses presented to the MSAC and PBAC ESCs (MSAC Application [1407](#)).

The ADAR assumed that 80% of patients would be able to tolerate a tissue rebiopsy. This was cited from MSAC Application 1721. The commentary noted that the 80% rate applied in MSAC Application 1721 referred to the success of testing following rebiopsy, rather than the proportion able to undergo a rebiopsy (which was assumed to be 100%). Though the commentary also noted that this was an assumption based on a prior MSAC consideration (MSAC Application 1407) that the rate of rebiopsy after first-line treatment would be 63% (and so a higher rate would apply prior to first-line treatment initiation).

Tissue biopsy was also assumed to follow negative ctDNA testing results, in all patients where this was able to be performed, to mitigate the impact of FN results. The commentary considered that while this assumption was consistent with RCPA best practice recommendations (Cooper et al. 2025)⁶⁹, the circumstances of use were not explored. The ADAR did reasonably exclude some patients from requiring a subsequent rebiopsy, though other patients could have been considered (e.g. patients with non-actionable alterations, or those diagnosed with early-stage disease who do not experience disease recurrence). However, real-world adherence to the best practice recommendations was not considered; it may be unlikely that complete adherence is observed. Sensitivity analyses resulting in cost-savings (i.e. dominant ICERs) may be observed with reduced use of rebiopsy following a negative result.

The analyses were also sensitive to estimates that affect the yield of ctDNA testing, including the performance of testing and factors that may result in patients being tested, but not receiving targeted treatment, including being tested at early-stage disease without advanced disease recurrence (which is likely to increase following the implementation of the lung cancer screening

⁶⁷ Department of Health 2016, *Manual of resource items and their associated unit costs.*, Commonwealth of Australia, Canberra, viewed Aug 2025, <https://www.pbs.gov.au/info/industry/useful-resources/manual>.

⁶⁸ <https://www.msac.gov.au/applications/1660>

⁶⁹ Cooper WA, et al 2025. Molecular testing of lung cancer in Australia: consensus best practice recommendations from the Royal College of Pathologists of Australasia in collaboration with the Thoracic Oncology Group of Australasia. *Pathology* 57(4): 425-436.

program), deterioration in performance status between testing and treatment initiation, or the presence of concurrent alterations in actionable genes (which have been reported in 8% of patients) (Passaro et al. 2021)⁷⁰.

The biomarker-specific estimates of yield and test performance applied in the economic evaluation for population 2 are presented in Table 34.

Table 34 Yield and test performance estimates applied in the economic evaluation (population 2)

	Yield of tissue testing (Table 30)	PPA	NPA	Concordant positives	Discordant positives	Adjusted yield ctDNA testing	False negatives
<i>EGFR</i>	17.9%	83%	98%	14.9%	1.6%	16.5%	3.0%
<i>ALK</i>	3.0%	65%	100%	2.0%	0.0%	2.0%	1.1%
<i>ROS1</i>	1.6%	45%	100%	0.7%	0.0%	0.7%	0.9%
<i>METex14sk</i>	3.6%	52%	99%	1.9%	1.0%	2.8%	1.7%
<i>NTRK</i>	0.23%	48%	99%	0.1%	1.0%	1.1%	0.1%
<i>RET</i>	1.7%	72%	99%	1.2%	1.0%	2.2%	0.5%
Total	28.0%	–	–	20.7%	4.6%	25.3%	7.3%
Total, adjusted for advanced disease^a	25.6%	–	–	19.3%	3.9%	23.2%	6.3%

ALK = ALK receptor tyrosine kinase; *EGFR* = epidermal growth factor receptor; *METex14sk* = MET proto-oncogene, receptor tyrosine kinase exon 14 skipping; *NPA* = negative percent agreement; *NTRK* = neurotrophic receptor tyrosine kinase; *PPA* = positive percent agreement; *RET* = ret proto-oncogene; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase

^a Calculated as *EGFR* variants + 75.9% × (*ALK* + *ROS1* + *METex14sk* + *NTRK* + *RET*)

Source: Table 76 and Table 77 of the ADAR.

The commentary noted that while the overall ratio of concordant to discordant positives modelled in the base case was approximately 5 : 1, for some biomarkers, this ratio reduced to approximately 1 : 1 (*RET*) or 1 : 10 (*NTRK*). The commentary further considered that interpretation of discordant positive results was not clear as it was not known whether these patients would respond to targeted therapy similarly to concordant positives and therefore, it was unclear whether reasonable inferences could be made regarding the cost-effectiveness for these additional patients treated.

The results of key scenario and univariate sensitivity analyses for population 2 are summarised in Table 35 for the ADAR base case, and Table 36 for the PASC-preferred scenario.

⁷⁰ Passaro, A, Attili, et al 2021, 'Genomic Characterization of Concurrent Alterations in Non-Small Cell Lung Cancer (NSCLC) Harboring Actionable Mutations', *Cancers (Basel)*, vol. 13, no. 9, Apr 30.

Table 35 Scenario and sensitivity analyses (population 2)

Analyses	Incremental cost	Incremental actionable alterations	ICER (\$/per additional actionable alteration)	% change in ICER
ADAR's base case (ctDNA-first scenario)	\$503	10.4%	\$4,827	–
Cost of rebiopsy (base case: \$11,408 based on IHACPA price weights, assuming 14% complication rate and 100% inpatient procedures)				
\$6,232 (NHCCDC, 14% complication rate)	\$1,551	10.4%	\$14,893	+209%
\$5,726 (NHCCDC, 10% complication rate)	\$1,654	10.4%	\$15,878	+229%
\$10,972 (IHACPA, 10% complication rate)	\$591	10.4%	\$5,675	+18%
\$7,657 (50% inpatient, 50% outpatient) ^a	\$1,263	10.4%	\$12,123	+151%
Use of tissue biopsy (base case: 80%) ^b				
0%	\$3,000	23.2%	\$12,932	+9%
100%	–\$121	7.2%	Dominant	–
40% after negative ctDNA result	–\$3,179	9.0%	Dominant	–
CtDNA testing PPA (base case: ADAR meta-analysis)				
Ontario Health ⁶⁵ estimates	\$663	9.6%	\$6,924	+43%
Patient attrition between testing and treatment (base case: 0%)				
5%	\$503	9.1%	\$5,517	+14%
10%	\$503	7.8%	\$6,438	+33%
Proportion of patients with advanced disease (base case: 75.9%) ^c				
100.0%	\$503	11.5%	\$4,365	–10%
58.0%	\$503	9.6%	\$5,239	+9%
47.5%	\$503	9.1%	\$5,514	+14%
Scenario analyses				
Expanding actionable alterations to include BRAF	\$419	10.6%	\$3,954	–18%
Expanding actionable alterations to include ERBB2 (HER2) and BRAF	\$157	11.7%	\$1,351	–72%
Expanding actionable alterations to include ERBB2 (HER2), BRAF and KRAS	–\$1,182	15.6%	Dominant	–
Updated analyses as presented in the applicant's pre-ESC response				
Cost of rebiopsy \$7,249.68 (NHCCDC, 14% complication rate)	\$1,345	10.4%	\$12,914	+168%
Multivariate analyses requested by ESC pre-ESC (department calculations)				
Cost of rebiopsy \$6,232 as per COM (BC \$11,408) and 100% inpatient (BC)				
50% inpatient	\$1,787	10.4%	\$17,155	+255%
33% inpatient	\$1,867	10.4%	\$17,925	+271%
30% inpatient (1721 PSD)	\$1,881	10.4%	\$18,061	+274%
10% inpatient	\$1,976	10.4%	\$18,966	+293%
Cost of rebiopsy \$7,249.688 as per COM (BC \$11,408) and 100% inpatient (BC)				
50% inpatient	\$1,684	10.4%	\$16,166	+235%
33% inpatient	\$1,799	10.4%	\$17,272	+258%
30% inpatient (1721 PSD)	\$1,820	10.4%	\$17,467	+262%

Analyses	Incremental cost	Incremental actionable alterations	ICER (\$/per additional actionable alteration)	% change in ICER
10% inpatient	\$1,955	10.4%	\$18,768	+289%
Applicant's pre-MSAC response: Updated ADAR base case: advanced disease only, ctDNA test first, rebiopsy cost \$7,250, ctDNA test cost \$3,000)				
Updated ADAR base case	\$1,345.30	11.5%	\$11,678.62	0%
Expand actionable alterations to include <i>BRAF</i>	\$1,345.30	12.6%	\$10,655.69	-9%
Expand actionable alterations to include <i>ERBB2 (HER2) + BRAF</i>	\$1,345.30	13.8%	\$9,717.32	-17%
Expand actionable alterations to include <i>ERBB2 (HER2) + BRAF + KRAS</i>	\$1,345.30	22.6%	\$5,965.10	-49%
Updated ADAR base case with ctDNA test cost \$2,500	\$845.30	11.5%	\$7,338.09	-37%
Updated ADAR base case with ctDNA test cost \$2,200	\$545.30	11.5%	\$4,733.78	-59%

ADAR= applicant developed assessment report; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; *ERBB2 (HER2)* = erb-b2 receptor tyrosine kinase 2 (previously known as *HER2*); ICER = incremental cost-effectiveness ratio; IHACPA = Independent Health and Aged Care Pricing Authority; *KRAS* = KRAS proto-oncogene, GTPase; NHCCDC = National Hospital Cost Data Collection; PPA = positive percent agreement

Note: Analyses in *italics* text were conducted during the evaluation. While the ADAR did present analyses expanding the actionable alterations to include *ERBB2 (HER2)*, *BRAF* and *KRAS*, revised estimates for *BRAF* and *KRAS* yield were applied.

^a Assuming an outpatient cost of biopsy of \$3,905

^b upfront in the comparator arm of the model, or after a negative ctDNA testing result in the intervention arm.

^c The base case assumes that 65.5% of patients are diagnosed with advanced disease and that 30% of those diagnosed with early-stage disease will progress. The sensitivity analyses assume the proportion of patients diagnosed with advanced disease decreases to 40% (40% + 60% × 30% = 58.0%) and 25% (25% + 75% × 30% = 47.5%), respectively, due to the lung cancer screening program.

Source: Constructed during the evaluation from Table 87 and Table 90 of the ADAR.

Table 36 Scenario and sensitivity analyses conducted by the commentary (population 2, PASC-preferred scenario)

Analyses	Incremental cost	Incremental actionable alterations	ICER (\$/per additional actionable alteration)	% change in ICER
PASC-preferred base case (tissue-first scenario)	\$3,000	25.3%	\$11,846	-
<i>CtDNA testing PPA (base case: ADAR meta-analysis)</i>				
<i>Ontario Health⁶⁵ estimates</i>	<i>\$3,000</i>	<i>23.7%</i>	<i>\$12,656</i>	<i>7%</i>
<i>Patient attrition between testing and treatment (base case: 0%)</i>				
<i>5%</i>	<i>\$3,000</i>	<i>24.1%</i>	<i>\$12,470</i>	<i>5%</i>
<i>10%</i>	<i>\$3,000</i>	<i>22.8%</i>	<i>\$13,162</i>	<i>11%</i>
Scenario analyses				
<i>Expanding actionable alterations to include BRAF V600E</i>	<i>\$3,000</i>	<i>26.2%</i>	<i>\$11,463</i>	<i>-3%</i>
<i>Expanding actionable alterations to include ERBB2 (HER2) and BRAF V600E</i>	<i>\$3,000</i>	<i>28.8%</i>	<i>\$10,407</i>	<i>-12%</i>
<i>Expanding actionable alterations to include ERBB2 (HER2), BRAF V600E and KRAS G12C</i>	<i>\$3,000</i>	<i>42.4%</i>	<i>\$7,073</i>	<i>-40%</i>

BRAF = B-Raf proto-oncogene, serine/threonine kinase; *ERBB2 (HER2)* = erb-b2 receptor tyrosine kinase 2 (previously known as *HER2*); ICER = incremental cost-effectiveness ratio; *KRAS* = KRAS proto-oncogene, GTPase; PPA = positive percent agreement

Note: Analyses in *italics* text were conducted during the evaluation.

Source: Constructed during the evaluation.

Population 3

In population 3, patients modelled were those with NSCLC who had progressed on targeted therapy and in whom tissue biopsy is not feasible or has failed. The commentary considered that while this was consistent with the wording of the proposed item descriptors in the ADAR, as noted in 'Proposal for public funding' for population 3, the PICO Confirmation proposed that this population be restricted to patients who had received one line of targeted therapy. The evidence presented in the ADAR for population 3 reflected patients who had received one line of targeted therapy (as noted in 'Proposal for public funding').

In patients with NSCLC who have progressed on targeted therapy and in whom tissue biopsy is not feasible or has failed, the modelled impact of ctDNA testing was to:

- improve equity of testing in patients in whom tissue rebiopsy is not feasible or had failed; and
- enable access to broader panel testing after disease progression.

The commentary considered that by restricting broader panel testing after disease progression to only those in whom tissue biopsy and testing are not feasible or had failed may incentivise the use of ctDNA testing where tissue biopsy would have been feasible.

The key inputs used in the economic evaluation for population 3 are presented in Table 37.

Table 37 Summary of the model inputs (population 3)

Input	Value applied (source)	Comment
Success of ctDNA testing	100% (Aggarwal et al. 2019)	As described in Table 27, reasons for test failure may require a new sample (and professional attendance) to be obtained. However, the impact of this is minor.
Yield of actionable alterations	68.0% (Park et al. 2021) ⁵⁰	The commentary noted that the estimates from Park et al. (2021) ⁵⁰ were not reliable due to the small number of patients included and had unlikely applicability to the proposed setting.
ctDNA test cost	\$3,000 (proposed fee)	As described in Table 27, the cost of an additional consultation to review results may also apply.

NSCLC = non-small cell lung cancer
Source: Adapted from Table 74 of the ADAR.

The results of the economic evaluation for population 3 are presented in Table 38.

Table 38 Results of the economic evaluation (population 3)

	ctDNA testing	SOC	Increment
Cost of ctDNA test	\$3,000.00	\$0.00	\$3,000.00
Actionable alterations identified	68.0% ^a	0.0%	68.0%
Incremental cost per actionable alteration identified			\$4,412

SOC = standard of care

^a Calculated from the success of ctDNA testing (100.0%) × yield of actionable variants (68.0%) (see Table 37).

Source: Adapted from Table 84 and Table 86 of the ADAR.

The key driver of the analysis is the yield of actionable alterations. The estimate used in the ADAR's base case analysis was directly taken from a small Korean study (Park et al. 2021)⁵⁰.

The commentary considered that due to the small patient numbers enrolled and differences in biomarker frequencies between non-Asian and Asian populations, this estimate has unlikely

applicability to the proposed setting and does not provide a reliable basis for estimating the benefit of ctDNA testing in progressed patients.

The commentary noted that alternate sources to inform the yield of actionable variants were not considered in the ADAR and that Sabari et al. (2019) may provide a more applicable estimate, as this was performed in the US and Australia. This study reported that 33.3% of patients would have a variant relevant to a targeted therapy available in Australia. Therefore, the yield following testing in this population was considered by the commentary to have been substantially overestimated.

The results of key scenario and univariate sensitivity analyses for population 3 are summarised in Table 39.

Table 39 Scenario and sensitivity analyses (population 3)

Analyses	Incremental cost	Incremental actionable alterations	ICER per additional actionable alteration	% change in ICER
ADAR's base case	\$3,000	68.0%	\$4,412	–
<i>Yield, base case: 68.0%</i>				
<i>33.3% (Sabari et al. 2019)</i>	<i>\$3,000</i>	<i>33.3%</i>	<i>\$9,009</i>	<i>+104%</i>
Scenario analyses (base case: tissue testing first, rebiopsy cost \$11,408)				
<i>ctDNA testing first, assuming 25% receive tissue testing^a</i>	<i>\$865</i>	<i>50.7%</i>	<i>\$1,705</i>	<i>–61%</i>
<i>ctDNA testing first, assuming 63% receive tissue testing^a</i>	<i>–\$2,381</i>	<i>24.5%</i>	<i>Dominant</i>	<i>–</i>
<i>ctDNA testing first, assuming 25% receive tissue testing^a and reduced biopsy cost (\$6,232, Table 33)</i>	<i>\$1,744</i>	<i>50.7%</i>	<i>\$3,439</i>	<i>–22%</i>
<i>ctDNA testing first, assuming 63% receive tissue testing^a and reduced biopsy cost (\$6,232, Table 33)</i>	<i>–\$164</i>	<i>24.5%</i>	<i>Dominant</i>	<i>–</i>

ICER = incremental cost-effectiveness ratio

^a upfront in the comparator arm of the model, or after a negative ctDNA testing result in the intervention arm.

Note: Analyses in *italics* text were conducted during the evaluation.

Source: Constructed during the evaluation from Table 89 of the ADAR.

The main driver of the incremental cost in the ctDNA testing first scenarios is the cost of tissue biopsy. When the lower cost per biopsy procedure is applied, cost savings are only assumed in the scenario with the highest uptake of tissue biopsy. The commentary noted that scenario analyses were unable to be revised during the evaluation to observe the impact of reduced yield, as a more applicable estimate of yield from tissue-based testing could not be identified.

14. Financial/budgetary impacts

For each of the proposed populations, the ADAR has used an epidemiological approach to estimate the financial implications of listing ctDNA testing genetic testing in NSCLC. The key sources of data used were lung cancer incidence and prevalence estimates, reported by the AIHW, published literature and expert opinion.

The financial implications to the MBS estimated in the ADAR resulting from the proposed listing of ctDNA testing genetic testing in NSCLC are summarised in

Table 40.

Table 40 Net financial implications of ctDNA testing genetic testing in NSCLC to the MBS

	2026	2027	2028	2029	2030	2031
Population 1						
Lung cancer incidence (AIHW 2024) ⁷¹ [A]	16,092	16,497	16,896	17,250	17,591	17,933
No. lung cancer cases, including those diagnosed clinically (incidence represents 90% ^a of cases) [B]	17,880	18,330	18,773	19,167	19,546	19,926
No. patients suspected NSCLC (B – A) [C]	1,788	1,833	1,877	1,917	1,955	1,993
Population 2						
Lung cancer incidence (AIHW 2024) ⁷¹	16,092	16,497	16,896	17,250	17,591	17,933
No. patients with NSCLC (86.6%, Mitchell et al. (2013) ⁶⁶)	13,936	14,286	14,632	14,939	15,234	15,530
Patients with insufficient tissue from initial biopsy (23.6%, Fielding et al. (2024) ⁵⁴) [D]	3,289	3,372	3,453	3,525	3,595	3,665
Population 3						
Lung cancer prevalence (0.1% ^b of the population)	27,806	28,201	28,581	28,946	29,295	29,628
No. prevalent NSCLC (86.6%, Mitchell et al. (2013) ⁶⁶)	24,080	24,422	24,751	25,068	25,369	25,658
No. prevalent patients on 1L targeted therapy (30% ^a)	7,224	7,327	7,425	7,520	7,611	7,697
No. patients who progress (30%, MSAC 1721) [E]	2,167	2,198	2,228	2,256	2,283	2,309
No. able to tolerate a rebiopsy (25% ^a)	542	549	557	564	571	577
No. successfully tested after rebiopsy (96%, Lee et al (2019) ⁷²) [F]	520	528	535	541	548	554
No. patients in whom tissue biopsy was not possible or failed (E – F) [G]	1,647	1,670	1,693	1,715	1,735	1,755
Total patients eligible (C + D + G)	6,724	6,875	7,023	7,157	7,285	7,413
Uptake of ctDNA testing (assumption)	50%	75%	90%	90%	90%	90%
No. patients who uptake ctDNA testing	3,362	5,156	6,321	6,441	6,557	6,671

⁷¹ Australian Institute of Health and Welfare [AIHW] 2024, *Cancer Data in Australia. Book 1e – Long-term cancer incidence projections*, AIHW, Canberra, viewed August 2025, <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/>.

⁷² Lee, K, et al 2019, 'Repeat biopsy procedures and T790M rates after afatinib, gefitinib, or erlotinib therapy in patients with lung cancer', *Lung Cancer*, vol. 130, Apr, pp. 87-92.

	2026	2027	2028	2029	2030	2031
Cost to MBS (85% schedule fee = \$2,897.60 per service)	\$9,741,545	\$14,940,893	\$18,316,072	\$18,663,712	\$18,998,124	\$19,330,967
Reduction in tissue-based testing (15.5% reduction in Population 2 patients who uptake ctDNA testing) ^c	-255	-391	-481	-491	-501	-511
Reduction in cost to MBS of tissue-based testing (\$1,098.87 per service) ^d	-\$279,693	-\$430,099	-\$528,602	-\$539,677	-\$550,345	-\$561,045
Net cost to the MBS	\$9,461,852	\$14,510,794	\$17,787,471	\$18,124,035	\$18,447,779	\$18,769,923

1L = first-line; MBS= Medicare Benefits Schedule; NSCLC = non-small cell lung cancer.

^a Key opinion leader feedback

^b The crude prevalence rate of lung cancer was calculated by the applicant by dividing prevalent cases of lung cancer reported by the AIHW (26,356) in 2020 and Australian population reported by the ABS (25,687,041) in 2020

^c Of those patients who uptake ctDNA testing in population 2, 80% (proportion able to tolerate a tissue rebiopsy) × 76.4% (proportion of patients able to be successfully tested) were assumed to otherwise have received tissue-based testing (61.2%). Following a negative ctDNA testing result (74.7% of patients tested), the ADAR assumed that 61.2% (i.e. proportion successfully tested following tissue rebiopsy) would receive tissue-based testing. The net reduction in tissue-based tests was estimated as 74.7% × 61.2% (45.6%) – 61.2%.

^d A weighted schedule fee was estimated based on MBS statistics for items 73437, 73438 and 73439 (November 2023–June 2024) (89% combined panel, 9% DNA panel only, 2% DNA then RNA panel) (\$1,201.27). As the 85% rebate based on this weighted schedule fee exceeded the Greatest Permissible Gap (\$102.40), the ADAR assumed the maximum copayment would apply.

Source: Constructed during the evaluation from Tables 94–100 and Table 103 of the ADAR.

The following issues were noted in the commentary regarding the estimates used to derive the eligible populations:

- Population 1: The ADAR assumed that ctDNA testing would be used in patients with lung cancer in whom tissue confirmation of disease was not feasible. The commentary considered that, based on the clinical evaluation, patients suspected of NSCLC may also include other diagnoses and so the use and cost to the MBS presented in the ADAR may be underestimated.
- Population 2: The ADAR assumed that ctDNA testing would replace tissue rebiopsy in patients regardless of disease stage. PASC advised that ctDNA testing should be restricted to those patients with advanced disease where tissue rebiopsy was not feasible or had failed. The commentary considered that use and cost to the MBS of ctDNA testing and reduction in tissue-based testing have been overestimated, relative to the PASC-preferred scenario.
- Population 3: The ADAR assumed that 30% of prevalent patients would receive targeted therapy for advanced disease. The commentary considered that this may not be reasonable, as the ADAR had not considered that patients diagnosed with early-stage disease would reflect a substantial proportion of prevalent patients. Furthermore, the ADAR assumed that 25% of patients would be able to tolerate a rebiopsy. The commentary noted that this was lower than previously considered by MSAC (63%, MSAC Application 1407). On this basis, the commentary considered that use and cost to the MBS may be overestimated, though acknowledged a substantial risk that ctDNA testing would be used in patients able to tolerate a biopsy due to the convenience and reduced test turnaround time. The extent of this use was not clear.

The commentary presented revised estimates of the cost to the MBS accounting for some of these issues (Table 41).

Table 41 Net financial implications of ctDNA testing genetic testing in NSCLC to the MBS, commentary

	2026	2027	2028	2029	2030	2031
Number of patients eligible						
• Population 1	2,244	2,301	2,356	2,406	2,453	2,501
• Population 2	979	1,003	1,027	1,049	1,070	1,090
• Population 3	502	515	527	538	549	560
Total patients eligible	3,725	3,819	3,911	3,993	4,072	4,151
Uptake of ctDNA testing	50%	75%	90%	90%	90%	90%
No. patients who uptake testing	1,862	2,864	3,520	3,594	3,665	3,736
Cost to MBS (\$2,897.60 per service)	\$5,396,525	\$8,298,516	\$10,199,070	\$10,412,758	\$10,618,599	\$10,825,043

MBS= Medicare Benefits Schedule; NSCLC = non-small cell lung cancer
 Source: Constructed during the evaluation from 'Attachment 4_MSAC 1798 Financial model.xlsx' to the ADAR.

In addition to impacts to the MBS, the ADAR estimated that ctDNA testing genetic testing in NSCLC would change the use and cost of tissue biopsy procedures to hospital budgets; and change the number of patients using targeted therapies. The commentary considered that if ctDNA testing was restricted—as per PASC advice—to only those who cannot tolerate a tissue rebiopsy, or in whom tissue rebiopsy has failed, there would be no change in the number of tissue biopsies performed.

The commentary noted that the approach used to estimate the net change in patients eligible for targeted therapy following ctDNA testing (Table 42) was in general reasonable for populations 1 and 2.

In population 3, the ADAR assumed the yield from ctDNA testing was based on Park et al. (2021)⁵⁰ which the commentary noted was not applicable to the proposed setting as it was based on a small number of Asian patients. Compared to a study conducted in Australian or US patients (Sabari et al. 2019), the yield applied was considered to have been substantially overestimated.

Table 42 Net change in the number of eligible patients for PBS-listed targeted therapy

	2026	2027	2028	2029	2030	2031
ADAR estimates						
• Population 1	153	235	289	295	301	307
• Population 2	171	263	324	331	337	344
• Population 3	420	639	777	787	797	806
Change in patients eligible for targeted therapy	745	1,138	1,390	1,413	1,435	1,457
Commentary revised estimates						
• Population 1	185	284	349	356	363	370
• Population 2	128	197	242	247	252	257
• Population 3	84	129	158	161	165	168
Change in patients eligible for targeted therapy	396	609	749	765	780	795

PBS = Pharmaceutical Benefits Scheme
 Source: Constructed during the evaluation from Tables 106–108 of the ADAR and 'Attachment 4_MSAC 1798 Financial model.xlsx'.

The commentary considered that the ADAR did not estimate the change in cost to the PBS or consider changes in use or cost of other resources due to changes in treatment, as specified in the PICO.

15. Other relevant information

The ADAR did not include an "other considerations" section.

If ctDNA testing NGS becomes available for patients "in whom tissue testing is not an option or has failed," there is a risk of ctDNA testing being used outside the intended population (i.e. leakage or test selection shifting). Its benefits—being safer, less invasive, and faster—may make it more appealing to both patients and clinicians than traditional tissue biopsy.

To help prevent this shift, PASC had advised revising the item descriptor to: "patients whose initial tissue biopsy is insufficient for tissue-based genetic testing or has failed." This change may reduce risk of inappropriate use.

Access to tissue biopsy is also limited by geography, as it is typically performed in metropolitan hospitals. CtDNA testing may offer a more accessible alternative, which could further contribute to use outside the intended population. It should be clarified whether limited access due to geographic location qualifies as a valid reason for tissue testing being unavailable, thereby justifying the use of ctDNA testing.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- ESC queried the comparative test performance of ctDNA testing-based genetic testing (measuring circulating tumour deoxyribonucleic acid [ctDNA]) versus tumour tissue-based genetic testing, in non-small cell lung cancer (NSCLC). ESC considered that relying on ctDNA testing to guide targeted treatments in patients with NSCLC may miss critical genetic alterations present in tissue. ESC noted important challenges and limitations with ctDNA testing: (1) low ctDNA fraction and variable shedding, especially in early-stage disease, could lead to false negatives; and (2) discordant/inconsistent genetic alterations identified from ctDNA testing and tumour biopsy due to tumour heterogeneity and sampling bias. Both of these lead to uncertain prognostic and predictive value for ctDNA testing. ESC noted that ctDNA testing-based testing is not currently routinely used as a frontline diagnostic test in NSCLC. ESC noted that there was limited evidence that ctDNA-positive but tumour-negative results would improve patient management or health outcomes, or that patients who test positive with ctDNA only would experience the same therapeutic benefit as patients who test positive with tumour tissue.
- Population 1 (suspected NSCLC): The ADAR's proposed population 1 was inconsistent with the PASC-ratified population 1. ESC noted that PASC had advised against the inclusion of population 1. In addition, patients would not have access to PBS subsidised medicines even if found to carry a genetic variant, because current PBS restrictions for targeted therapies require patients to be histologically or cytologically confirmed to have NSCLC to access the medicines. Therefore, ESC considered for this population a separate and distinct codependency exists which needs to be assessed via a PBAC/MSAC codependent application. There is currently little clinical evidence for this population, which affects the economic evaluation. There is also high risk of use of the test outside the intended population.

- **Population 2 (newly diagnosed NSCLC):** ESC noted that the ADAR's proposed population 2 (any disease stage) was broader than the PASC-ratified population 2 (unresectable or metastatic disease). ESC noted it was most likely that surgical resection would not be feasible in patients at earlier stages of disease and therefore tumour tissue would be more difficult to access. There is also little supportive evidence that ctDNA testing would lead to improved health outcomes for early-stage disease. ESC noted that the ADAR had largely ignored PASC's advice that ctDNA testing should be used as a second-line test when the initial tissue-based genetic testing has (1) either failed or the biopsy tissue was insufficient and (2) rebiopsy is not possible. Rather, the ADAR proposed that most failed tissue-based patients would have ctDNA based-testing rather than a rebiopsy. ESC considered that the ADAR had not adequately addressed the issue of discordance between ctDNA testing-based and tumour tissue-based genetic testing, nor the impact of this discordance on change in clinical management, comparative safety and clinical effectiveness. ESC considered that use outside the PASC-ratified population was likely to occur, especially because ctDNA testing as a less invasive procedure (venepuncture) would be perceived as a more convenient procedure compared to tissue rebiopsy.
- **Population 3 (progressing NSCLC):** ESC considered the ADAR's proposed population 3 to be problematic. ESC noted that if a genetic alteration is identified at diagnosis, there is a low likelihood of a patient subsequently developing a new (different) genetic alteration that is actionable. Further, there is currently only one second-line targeted therapy (osimertinib) available on the PBS, which is now mostly used as first-line therapy.
- ESC further noted that the recently introduced National Lung Cancer Screening Program might identify patients with small lesions that cannot be biopsied owing to size or location, and that these patients have not been accounted for in the ADAR.

MBS item descriptors and fee

- The issues with the populations are also reflected in the ADAR's proposed MBS item descriptors which lack appropriate detail regarding stage of disease and/or the requirement that ctDNA testing is only used if rebiopsy and tissue-based genetic testing fails or is not possible.
- The ADAR proposed an MBS fee of \$3,000 for the ctDNA test, which ESC considered was high. ESC considered it was not appropriate to benchmark the MBS fee for ctDNA against MBS item 73307⁷³ (homologous recombination deficiency status testing), as proposed by the applicant. ESC noted the MBS fee of \$1,247.00 recently supported by MSAC for MBS item 73437⁷⁴ for an NGS panel test for NSCLC (MSAC application 1721). Although not a ctDNA based testing item, ESC also noted the measurable residual disease testing by next-generation sequencing, MBS item 73310⁷⁵ used for molecular monitoring for both baseline and post treatment has a fee of \$1,550. ESC noted other similar current or soon to be accredited test costs and advised that an MBS fee of no more than \$1,500 would be appropriate.

Economic issues:

- PASC recommended a cost-utility analysis be conducted, but the ADAR instead presented ICERs for each population expressed as the incremental cost per additional actionable alteration identified. ESC was concerned with the ADAR's approach which essentially truncated the economic evaluation at the time of treatment decisions

⁷³ [Item 73307 | Medicare Benefits Schedule](#)

⁷⁴ [Item 73437 | Medicare Benefits Schedule](#)

⁷⁵ [Item 73310 | Medicare Benefits Schedule](#)

without defining what these might be. ESC therefore considered that the ADAR did not capture the downstream changes in costs and effectiveness that would be expected to accrue from changes in management as a result of the ctDNA testing test. ESC agreed with PASC that these impacts must be modelled given that the applicant is seeking reimbursement for a new biopsy that could in theory impact the treatment ICERs previously agreed by the PBAC for PBS-listed medicines, especially in the context of an expensive proposed test with claimed improvement in health outcomes and predicted increase in the utilisation of these medicines.

- The inconsistencies of the ADAR's 3 proposed populations versus the PASC-ratified populations flowed through to the economic evaluation and financial analyses. Notwithstanding ESC's concern regarding the lack of a cost-utility analysis, and hence the validity of the ADAR's economic evaluation, ESC noted the following:
 - The main driver of the ICER for population 1 was the yield estimate of 20.1% 'actionable alterations' for the base case. Lower yields, as suggested by the commentary, increased the ICER.
 - The main drivers for the ICER for population 2 were the cost of tissue rebiopsy (and complications) and the substitution of ctDNA biopsies for tissue rebiopsies. The ADAR estimated the cost of rebiopsy with or without complications based on the weighted National Efficient Price, but ESC agreed with the commentary that directly applying costs from the National Hospital Cost Data Collection (NHCD) report would be more appropriate, which increased the base case ICER. The assumption that all tissue biopsies would occur as inpatient procedures was also unsupported and reduced the ICER.
 - The ICER for population 3 was based on the proportion of 'actionable alterations' identified (68% from a Korean study). ESC considered that 68% is too high for the Australian context where an 'actionable alteration' would have already been identified in the setting of determining first-line therapy, and so the likelihood of a new 'actionable alteration' being identified on disease progression is low.

Financial issues:

- The cost to the MBS was likely overestimated in the ADAR; however, the overall cost to the Australian healthcare system was estimated in the commentary to be about \$redacted in Year 1 to \$redacted by Year 6, with most of the additional costs accruing to the PBS because of the potential increased utilisation of medicines.

Other issues:

- ESC noted that ctDNA testing would be more accessible for patients living in rural and remote areas compared to tissue biopsy testing.
- ESC was concerned that there are codependency issues associated with this application that have not been addressed in the ADAR. ESC did not agree with the applicant's emphasis on MSAC Application 1721 (small gene panel testing in NSCLC) as a precedent for the current application, and was of the view that MSAC Application 1782 (ctDNA testing-based testing in breast cancer) is a more relevant precedent. ESC noted that the majority of PBS restrictions for therapies targeting particular oncogenic drivers in NSCLC state that the sample type must be "in tumour material". ESC advised that if MSAC is of a mind to support the creation of MBS items for variant testing in ctDNA testing, MSAC should seek guidance from the PBAC regarding whether ctDNA in a ctDNA testing is considered "tumour material", and whether the relevant PBS restrictions (and related PBS pricing arrangements) would need to be altered as a consequence of any supportable MBS items for ctDNA testing in NSCLC patients.

- Given the current application has several significant issues that are unlikely to be resolved or adequately addressed prior to the November 2025 MSAC meeting, ESC requested the MSAC Executive consider whether this application should proceed to MSAC for consideration at its November 2025 meeting with issues remaining unresolved, or whether it should instead be considered as a PBAC/MSAC codependent application at a future date.

ESC discussion

The Evaluation Subcommittee (ESC) noted that the application requested Medicare Benefits Schedule (MBS) funding for ctDNA testing genetic testing using next-generation sequencing (NGS) for the characterisation of clinically actionable genetic alterations in patients with non-small cell lung cancer (NSCLC). ESC noted that the application was submitted by HTAnalysts on behalf of a cross-industry consortium consisting of AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo Australia, Illumina, SOPHiA Genetics and Thermo Fisher Scientific.

ESC noted that the application would be MSAC's first consideration of ctDNA testing using a multi-gene panel for the characterisation of actionable alterations in patients with NSCLC. ESC recalled that MSAC had previously supported the creation of new MBS items 73437, 73438 and 73439 for small NGS multi-gene panels for biomarker testing using tumour tissue in patients with NSCLC (MSAC Application 1721⁷⁶). ESC also recalled that in April 2025, MSAC had considered but did not support public funding of genetic testing to detect estrogen receptor 1 (ESR1) variants in ctDNA in patients with estrogen receptor positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer to determine eligibility for elacestrant on the Pharmaceutical Benefits Scheme (PBS) (MSAC Application 1782⁷⁷).

ESC noted that no additional pre-ESC consumer or organisation feedback was received for this application after the PASC stage. ESC noted genetic and genomic tests might cause significant anxiety for some patients and their families. Therefore, ESC considered that clear and effective communication for managing anxiety related to genetic and genomic testing is vital in clinical practice.

ESC noted that the TGA has approved one commercial test which is currently registered as a companion diagnostic IVD and several inhouse in vitro diagnostic (IVD) tests, and that testing is available through National Association of Testing Authorities (NATA) - accredited laboratories. There is currently no External Quality Assessment Program (EQAP) established in Australia for the proposed test, which ESC recommended should be in place if ctDNA testing is supported by MSAC.

ESC noted multiple issues with the ADAR's proposed populations, including various inconsistencies versus the PASC-ratified populations, with flow-on consequences for the economic and financial analyses.

For population 1 (suspected NSCLC), ESC noted that this was a population which PASC recommended to be excluded from the PICO Confirmation at its April 2025 meeting, owing to issues arising from the lack of a confirmed diagnosis of NSCLC in this population such as disease misclassification, diagnostic uncertainty, lack of PBS-funded medicines in the absence of a defined diagnosis, and insufficient clinical evidence. ESC noted that the majority of PBS restrictions for therapies targeting particular oncogenic drivers in NSCLC state that the sample

⁷⁶ <https://www.msac.gov.au/applications/1721>

⁷⁷ <https://www.msac.gov.au/applications/1782>

type must be “in tumour material”. ESC considered for this population a separate and distinct codependency exists which needs to be assessed via a codependent PBAC/MSAC application.

For population 2 (newly diagnosed NSCLC), ESC noted that PASC advised adding ‘unresectable or metastatic’ to the population definition as it was most likely that surgical resection would not be feasible in patients at this disease stage and therefore tumour tissue would be more difficult to access. ESC noted that the ADAR had largely ignored PASC’s advice that ctDNA testing should be used as a second-line test when the initial tissue-based genetic testing has (1) either failed or the biopsy tissue was insufficient and (2) rebiopsy is not possible.

For population 3 (relapsed/progressing NSCLC), ESC noted that an actionable alteration is typically identified at the time of diagnosis, with a minimal likelihood of subsequently developing an additional, distinct alteration. ESC noted even if there was a new distinct alteration, the likelihood of it being actionable (i.e., a change in therapy would result) is low due to there being only one second-line targeted therapy (osimertinib) currently available on the PBS, which is now largely being used as first-line. Therefore, ESC considered the proposed population 3 to be problematic.

ESC noted that the ADAR proposed two sets of MBS item descriptors for each population that are specific to determining eligibility for treatments listed under the PBS, as well as items that do not specify this purpose. ESC agreed with PASC that the proposed test should be restricted to identifying relevant gene variants and fusions to determine eligibility to PBS-funded targeted therapies.

ESC noted that the ADAR’s proposed item descriptors differed from the PASC-recommended item descriptors and the issues with the proposed populations are also reflected in the ADAR’s proposed MBS item descriptors.

For population 1, ESC highlighted that these patients currently would not have access to PBS funded medicines, even if an actionable alteration was identified.

For populations 2 and 3 proposed MBS item descriptors, ESC considered that the erb-b2 receptor tyrosine kinase 2 (*ERBB2*) (previously known as *HER2*) gene should be included on the gene panel, as this would align with Australian and international best practice. ESC noted that while there are currently no targeted therapies for this gene on the PBS, there are several currently being evaluated by the TGA. ESC considered that including ‘at least’ in the descriptor would further futureproof the MBS item as more genes and targets are being added. ESC also considered it may be appropriate to refer to ‘genetic alterations’ rather than listing all the currently known/identified oncogenic variants and fusions.

ESC agreed that ‘lung cancer’ should be removed from the proposed item descriptor to clarify the population is restricted to patients with ‘NSCLC’.

ESC also considered that NGS is superior to fluorescence in situ hybridisation (FISH) for testing multiple genes and recalled that MSAC had already supported NGS panels for NSCLC, citing superior effectiveness and safety compared to sequential single-gene testing (Application 1721). Furthermore, ESC noted FISH is not suitable for ctDNA testing, as ctDNA relies on fragmented circulating cell-free DNA while FISH test requires intact DNA.

ESC considered defining the patients who should be eligible for ctDNA testing is critical, and expressed concerns about potential inappropriate use of ctDNA testing citing that its safety, faster turnaround time (TAT), and convenience might lead to patients receiving the most convenient test rather than the most appropriate test.

ESC considered the ADAR’s proposed MBS fee of \$3,000 to be high and not justified and disagreed with benchmarking it against MBS item 73307 (homologous recombination deficiency

status testing, MBS fee \$3,000), as proposed by the applicant. ESC noted that the majority of similar services of existing pathology MBS items (e.g., MBS 73437, MBS fee \$1,247) with multi-gene panels using NGS methods (not by ctDNA) for varying numbers of genes tested across differing conditions have fees of no more than \$1,500, depending on the setting. There are currently no MBS items that allow ctDNA-based testing. Although not a ctDNA-based testing item, ESC also noted that MBS item 73310 (measurable residual disease testing by NGS) is used for molecular monitoring for both baseline and post treatment and has a fee of \$1,550. Therefore, ESC considered that an MBS fee no more than \$1,500 would be appropriate.

ESC advised that the MBS descriptors should not be 'pathologist determinable', as ctDNA testing requires freshly drawn samples and a specific blood collection tube, making it more appropriate for a specialist/consultant to request the test.

ESC advised that co-claiming restrictions, where appropriate, should be implemented if MSAC supports the application.

ESC advised that the MBS descriptors should limit testing to once per new diagnosis, as the chance of acquiring additional new variants after initial testing and diagnosis is extremely low. ESC noted this may not support using the test for molecular monitoring for residual or recurring disease, depending on a revised estimate of diagnostic yield and cost per diagnosis, and would make population 3 irrelevant.

Overall, ESC noted that the clinical evidence was derived from mostly prospective observational studies and meta-analyses, with some randomised controlled trial (RCT) - linked evidence for linked outcomes. ESC considered this evidence on test performance to be incomplete, with the evidence being weakest for survival outcomes, mainly due to the small sample sizes in the cohort studies. ESC also considered that the results across the clinical studies and across subgroups were:

- most consistent for specificity and TATs across all populations
- moderately consistent for sensitivity and clinical outcomes
- least consistent overall for populations 1 and 3.

ESC noted the applicability of the clinical evidence to the Australian setting as it aligns with Royal College of Pathologists of Australasia (RCPA)/Thoracic Oncology Group of Australasia (TOGA) guidelines and current clinical pathways.

ESC considered ctDNA testing would have no additional safety concerns as the sample (plasma) for testing would be obtained via a simple venepuncture, and therefore it has superior safety compared to tissue biopsy in this regard. However, ESC considered that potential safety issues related to false positive (FP) and false negative (FN) test results should be expected but were not addressed in the ADAR. ESC considered indirect harms from discordant results were real and so under-quantified. Furthermore, ESC noted evidence on long-term safety is not available due to the recent introduction of ctDNA testing. ESC, however, considered that the clinical claim of non-inferior safety of ctDNA-biopsy when compared with no testing, and superior safety when compared to tissue biopsy appeared reasonable.

ESC expressed significant concerns about the potential discordance in results between ctDNA testing-based and tumour tissue-based genetic testing. ESC considered that neither the ADAR nor the pre-ESC response adequately addressed the underlying causes for discordance between tumour and ctDNA testing.

- ESC considered that there were two primary factors that need to be considered: heterogeneity in the variants identifiable between different tumour sites in an individual;

and heterogeneity of variants identifiable in a single tumour site with a variable propensity to disperse into the circulation.

- Due to limited evidence presented, ESC raised concerns for scenarios where low ctDNA concentrations (e.g., from early-stage disease) and variable shedding could result in false negatives (FNs). Further, there is poor concordance between ctDNA- and tissue-based testing due to tumour heterogeneity and sampling bias. Both of these issues lead to uncertain prognostic and predictive value for ctDNA testing.
- Consequently, ESC queried the comparative test performance of ctDNA testing-based genetic testing versus tumour tissue-based genetic testing in NSCLC. ESC considered that relying on ctDNA testing to guide targeted treatments may miss critical genetic alterations present in tissue, leading to suboptimal therapeutic decisions.
- ESC also noted that guidelines⁷⁸ recommend confirming negative ctDNA results with tumour tissue testing before excluding targeted therapy options, reinforcing the perspective that ctDNA testing is complementary to rather than a replacement for tissue analysis. Tissue analysis remains the gold standard, and the clinical utility standard used in the clinical trials of the relevant PBS-funded medicines, so negative ctDNA findings should prompt tissue-based testing confirmation when feasible. ESC noted that this creates a problematic scenario, whereby patients in whom tissue biopsy is not feasible are subsequently required to undergo tissue biopsy.

For population 1 (suspected NSCLC), ESC agreed with PASC that this population should be excluded. ESC considered the evidence the ADAR presented for population 1 to be weak and uncertain.

- ESC noted that the ADAR presented limited clinical evidence regarding differential diagnoses in patients only suspected of having NSCLC. ESC considered that potential risk for misclassification exists in cases where patients have a different cancer diagnosis (such as lung cancer types other than NSCLC or cancers originating outside the lung) and present with a clinically actionable variant linked to NSCLC, particularly when there is no histological or cytological confirmation. ESC considered there is high risk of use of the test outside the intended population.
- ESC noted that there was no evidence presented to support the claim that the proposed test would lead to a change in management or improved therapeutic outcomes. ESC noted that there is currently insufficient evidence available to support change in management and therefore clinical decision-making in cases where test methods yield discordant results, particularly when a histological or cytological diagnosis for NSCLC is absent for patients who have positive ctDNA testing findings but negative tissue results. ESC considered that this would also result in a highly uncertain economic model and financial impact.
- ESC noted because under current PBS restrictions, population 1 would be unable to access any PBS-listed medicine irrespective of test results, due to the absence of histological or cytological confirmation of their diagnosis, such patients will continue to be initiated on standard chemotherapy, unless there is a TGA regulatory and/or PBS policy shift allowing them to access PBS medicines without a confirmed diagnosis of NSCLC.
- ESC acknowledged there may be a value of knowing associated with this patient group, as the comparator is no testing.

For population 2 (newly diagnosed NSCLC), ESC considered that for the PASC-recommended population 2, ctDNA testing is superior in effectiveness and safety compared to current standard

⁷⁸ <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450>.

of care where tissue-based testing failed and rebiopsy is not feasible. However, if tumour rebiopsy is available, ESC considered comparative clinical effectiveness is likely non-inferior.

- ESC noted the evidence for population 2 was more robust than for the other two proposed populations. Compared to the reference and clinical utility standard (tissue biopsy), the sensitivity for ctDNA testing was about 68%, specificity was about 89–90% and concordance was about 85%. Studies have demonstrated that 18–22% of patients who had a positive ctDNA testing benefitted from targeted therapy. ESC also noted the applicant's pre-ESC response regarding limited evidence on the accuracy of ctDNA testing in early-stage disease, and considered that the clinical benefit in testing during early-stage disease is not sufficiently established.
- The limited evidence presented for population 2 indicated that health outcomes, such as progression-free survival (PFS) and overall survival (OS), for patients treated based on ctDNA testing may be non-inferior to those treated based on tissue testing, particularly in patients who have insufficient tissue to test.
- ESC acknowledged that ctDNA testing has faster TATs than tissue biopsy and may benefit patients in rural and remote communities, which, in the absence of any evidence provided, may theoretically improve health outcomes if they can access relevant therapy faster. More likely, ESC noted that ctDNA testing-based genetic testing may identify additional patients eligible for targeted therapy who would otherwise miss out in the absence of any genetic testing.

For population 3 (progressing NSCLC), ESC considered the clinical claim of superior effectiveness and safety should be carefully interpreted as there was minimal evidence indicating a clinical benefit for this population.

- ESC noted the ADAR presented limited evidence for population 3 and test accuracy remains moderate for this population.
- ESC noted the comparator for population 3 is no molecular testing. ESC considered the yield of 68% 'actionable alterations' to be extremely overestimated; in reality, the probability of these patients acquiring a second, new actionable genetic variant after initial treatment failure is low.
- ESC noted immunotherapy use in this population may increase irrespective of ctDNA testing results.
- ESC disagreed with the ADAR's claim that a positive test could lead to accessing a second-line therapy, as the only relevant second-line PBS listed therapy is osimertinib (and this medicine is now largely used as first-line therapy); therefore, testing could lead to research [novel agent trial eligibility criteria] use. ESC acknowledged that, in theory, identification of a marker suggesting eligibility for targeted treatment is likely more effective than non-targeted or non-guided targeted treatment.

Overall, ESC noted that ctDNA testing has high specificity and moderate sensitivity for actionable alterations compared to tissue biopsy, and that the clinical benefit is strongest for newly diagnosed patients with insufficient tissue for molecular testing or failed tissue-based testing and for whom rebiopsy is not an option (population 2). Evidence is less robust (limited, as not tested currently) for suspected NSCLC without tissue confirmation (population 1) and for use after progression on targeted therapy (population 3).

ESC was concerned that there are codependency issues associated with this application that have not been addressed in the ADAR. ESC did not agree with the applicant's emphasis on MSAC Application 1721 (small gene panel testing in NSCLC) as a precedent for the current application, and was of the view that MSAC Application 1782 (ctDNA testing-based testing in breast cancer) is a more relevant precedent.

ESC noted that PASC had recommended a cost-utility analysis be conducted, but the ADAR had instead presented incremental cost-effectiveness ratios (ICERs) for each population expressed as the incremental cost per additional 'actionable alteration' identified. ESC was concerned that the approach in the ADAR essentially truncates the economic evaluation at the time of treatment decisions without defining what these might be. ESC therefore considered that the ADAR did not capture the downstream changes in costs and effectiveness that would be expected to accrue from changes in management as a result of the ctDNA testing. ESC agreed with PASC that these impacts must be modelled given that the applicant is seeking reimbursement for a new biopsy that could in theory impact the treatment ICERs previously agreed by the PBAC for PBS-listed medicines, especially in the context of an expensive proposed test with claimed improvement in health outcomes and predicted increase in the utilisation of these medicines.

Across all 3 populations, ESC noted that the incremental yield of 'actionable alterations' identified was a main driver of the modelled incremental cost-effectiveness. The proposed fee for ctDNA testing (which ESC considered to be high and unjustified) was another key driver.

For population 1, ESC noted the ADAR presented an incremental cost-effectiveness ratio (ICER) of \$14,915 per 'actionable alteration' identified.

- ESC agreed with the commentary that interpretation of this cost-effectiveness outcome was unclear as the current TGA approvals and PBS restrictions for targeted therapies do not allow access to therapy by this population.
- ESC noted that it was possible, albeit a very small possibility, that ctDNA testing in patients only suspected of NSCLC could identify oncogenic variants in non-NSCLC patients.
- ESC noted that the ADAR's base case analysis applied an incremental yield estimate of 20.1% 'actionable alterations' which ESC considered too optimistic. ESC noted that using a lower yield estimate (e.g., 16% as suggested by the commentary) would increase (+26%) the ICER to \$18,750 per 'actionable alteration' identified.
- ESC further noted that restricting the testing population to those with advanced disease and identifying more 'actionable alterations' would result in lower ICERs.

For population 2, ESC noted that the ADAR's base case ICER was \$4,827 per 'actionable alteration' identified.

- ESC considered that the costing of rebiopsy and complications should be based on the National Hospital Cost Data Collection (NHCDC) report for rebiopsy costs (which is \$6,232, not \$11,408 as used in the ADAR), which increased the base case ICER to \$14,893 per 'actionable alteration' (+209%). ESC noted the lower ICER presented in the ADAR was driven by the substitution of more expensive tissue biopsies with ctDNA testing because of the setting and rates of complications, but there is little Australian evidence to inform this.
- ESC noted that, in its pre-ESC response, the applicant agreed that the cost of rebiopsy originally used in the ADAR was likely overestimated. The applicant therefore proposed that cost weights from the NHCDC report (2022–23) be used instead and applied against the current National Efficient Price for 2025–26. ESC noted when weighted by 2022–23 separations, and assuming a 14% complication rate and 100% inpatient procedures, this yields an updated re-biopsy cost of \$7,249.68, yielding a revised ICER of \$12,296.53 per actionable outcome.
- ESC queried whether all tissue biopsies are performed as inpatient services or if they can be performed as day procedures. ESC considered that assuming 100% of procedures require inpatient admission lacks face validity. Assuming 50% of tissue biopsies would

occur in the outpatient setting, ESC noted the ICER increased to \$12,123 per 'actionable alteration'.

This ICER also assumed that a negative ctDNA testing result would be followed by a tissue biopsy when possible, to ensure that cases are not missed, which is appropriate for those who can tolerate a tissue rebiopsy. ESC noted that, by reducing the number of rebiopsies, the ctDNA testing arm can become dominant. ESC noted that if patients cannot undergo rebiopsy, the ICER increased to \$12,932 per actionable outcome. Additionally, if rebiopsy is not feasible and ctDNA testing is used first, then for population 2, the ICER would increase since there would be no tissue biopsy offsets.

- ESC noted that the multiway sensitivity conducted by the commentary, when based on NHCDC data and 50% outpatient procedures, gives an ICER of \$17,155.29 per 'actionable alteration'. ESC noted the department conducted an additional sensitivity analysis based on 33% inpatient procedures, which resulted in an ICER of \$17,924.72 per 'actionable alteration'.
- ESC also noted that decreasing the cost of the ctDNA testing test to \$1,500 and using the rebiopsy costs proposed by the commentary results in an ICER of \$494 per 'actionable alteration'.

For population 3, ESC noted that the ADAR's presented an ICER \$4,412 per 'actionable alteration' identified.

- ESC noted these results were sensitive to the proportion of 'actionable alterations' identified (68% used in base case from a Korean study). The commentary considered that 68% was too high and not likely generalisable to the Australian context, and cited Sabari et al. (2019) as an alternate source, which stated that 33% would have a variant. ESC agreed that 33% was more appropriate, but considered that the likelihood of another new 'actionable alteration' being identified after an alteration had already been identified for first-line therapy would be smaller than 33%.

ESC considered that the ADAR's exclusion of the relatively small costs associated with medical practitioners ordering and delivering ctDNA testing test results was not appropriate and should have been included in the economic evaluations and financial estimates for all 3 populations.

ESC noted the ADAR used an epidemiological approach in its financial estimates.

When considering all 3 populations, the net cost to the MBS is estimated to be \$9,461,852 in Year 1, increasing to \$18,769,923 in Year 6.

ESC considered the costs may be underestimated for population 1 due to use outside the intended population and overestimated for population 3 because targeted therapy is only for patients with advanced disease stage and the 30% estimate used in the ADAR included patients with early-stage disease.

ESC also identified that there is an uncertain impact on ctDNA testing from the recently introduced National Lung Cancer Screening Program which may detect individuals with small lesions that cannot be biopsied due to its size or location. Therefore, the National Lung Cancer Screening Program in Australia may increase early-stage detections.

ESC noted the financial impact may decrease if the MBS item descriptor for population 2 recommended by PASC is used. Using the commentary's recalculations that considered these issues and the proposed MBS fee of \$2,897.60, the financial impact decreased to \$5,396,525 in Year 1 to \$10,825,043 in Year 6. ESC noted using an ESC suggested MBS fee of \$1,500 would further decrease the financial impact.

ESC agreed with PASC that the anticipated health benefits associated with ctDNA testing would occur only if there were changes to the restrictions of the PBS-listed therapies for NSCLC so patients could access them. ESC considered a positive ctDNA testing-based test result identifying a biomarker in the proposed patient population could effectively identify an additional subgroup of patients who would then be eligible for PBS-subsidised targeted therapy for NSCLC significantly increasing costs to the PBS. ESC noted the overall impact to the health system could be about \$redacted in Year 1 to \$redacted in Year 6.

Overall, ESC noted that the application requested public funding for a test with a much higher proposed MBS fee than other tests, with potential for high utilisation in the context of the National Lung Cancer Screening program. Apart from the issues pertaining to the tests (e.g., discordance between ctDNA testing-based (ctDNA) testing and tumour tissue-based genetic testing), ESC noted that the claimed health benefits associated with the proposed test could only occur via a codependent technology, i.e., a targeted treatment, via wider and possibly earlier identification and treatment. ESC noted that “A codependent submission is required when the Minister for Health requires advice from 2 different expert advisory committees because listing of the codependent technologies involves 2 separate reimbursement schemes. For example, codependent technologies that require new listings or amendments to both the PBS and the MBS (such as a genetic test to determine eligibility for a medicine) would need advice from both PBAC and MSAC” (TG 15.6, MSAC Guidelines⁷⁹). ESC noted that while the applicant was an industry-based consortium of selected genomic test manufacturers and pharmaceutical companies, the application was not submitted as part of an integrated codependent submission. ESC advised that if MSAC is of a mind to support the creation of MBS items for variant testing in ctDNA testing for NSCLC, MSAC should first seek guidance from the PBAC regarding whether the relevant PBS restrictions (and related pricing arrangements) would need to be altered as a consequence of any supportable MBS items for ctDNA testing in NSCLC patients (e.g., whether ctDNA in a ctDNA testing is considered “tumour material”). Given the current application has several significant issues that are unlikely to be resolved or adequately addressed prior to the November MSAC meeting, ESC requested the MSAC Executive to consider whether this application should proceed to MSAC for consideration at its November 2025 meeting with issues remaining unresolved, or whether it should instead be considered as a PBAC/MSAC codependent application at a future date.

17. Applicant comments on MSAC’s Public Summary Document

The sponsors of this application, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo Australia, Illumina, SOPHiA Genetics and Thermo Fisher Scientific, are disappointed by MSAC's decision not to support public funding of plasma based ctDNA testing to detect clinically actionable genetic alterations in patients with NSCLC. This outcome is regrettable given the clear and ongoing unmet clinical need, particularly for patients who cannot access adequate tumour tissue testing and who may therefore miss the opportunity to receive potentially life-extending targeted therapy. The sponsors sincerely thank the clinicians, professional organisations and consumer representatives who provided strong support for this application. We will continue to engage with government stakeholders, clinical experts and the patient community to progress solutions that will enable equitable access to ctDNA testing through the MBS, with the shared goal of ensuring more Australians can benefit from timely access to effective PBS-listed therapies.

⁷⁹ <https://www.msac.gov.au/sites/default/files/2024-10/guidelines-for-preparing-assessments-for-msac.pdf>

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)