

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1721 Small gene panel testing for NSCLC

Applicant: Royal College of Pathologists of Australasia
(RCPA)

Date of MSAC consideration: 24-25 November 2022

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 for small next generation sequencing (NGS) panels for biomarker testing of patients with non-squamous (or histology not otherwise specified) non-small cell lung cancer (NSCLC), was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health and Aged Care. In this case, biomarker testing is for the purposes of determining suitability for targeted treatments for non-squamous NSCLC, available through the Pharmaceutical Benefits Scheme (PBS).

The clinical claim is that the use of either a small combined deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) NGS panel, or sequential use of a DNA panel and (if required) an RNA panel, would be superior in effectiveness and safety compared to sequential single-gene testing for biomarkers in patients with NSCLC. This is due to a small panel (or two) making more efficient use of tumour tissue, resulting in fewer re-biopsies being required, a more rapid turnaround time, and faster initiation of targeted treatment.

This Department Contracted Assessment Report (DCAR) assessed the safety, effectiveness, and cost-effectiveness of small NGS panels compared to sequential single gene testing, to provide the evidence-base for the Medical Services Advisory Committee (MSAC) to decide its advice regarding funding on the MBS.

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 supported the creation of new Medicare Benefits Schedule (MBS) items for small NGS panels for biomarker testing of patients with non-squamous (or histology not otherwise specified) NSCLC. MSAC did not support the expansion of the new test item to include patients with squamous NSCLC because it was rare for these patients to harbour the variants covered in the supported NSCLC panels. MSAC considered that the evidence for small gene panel testing demonstrated its superior effectiveness because of 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 re-biopsy compared with sequential single gene tests. MSAC considered there to be acceptable cost effectiveness and financial implications.

MSAC also supported amendments to the existing MBS items for sequential single gene tests.

Consumer summary

This is an application from the Royal College of Pathologists of Australasia requesting Medicare Benefits Schedule (MBS) listing of gene panel testing for people with non-squamous non-small cell lung cancer (NSCLC). This genetic testing is used to determine who can access certain types of drugs on the Pharmaceutical Benefits Scheme (PBS).

It is common for some types of cancers to have certain harmful genetic changes that can be used as targets for treatments. These targeted treatments don't work for people who do not have a target gene variant, so genetic testing is needed to determine if someone should receive a certain treatment or not. For NSCLC, the most common harmful gene variants are in the *EGFR*, *ALK*, *ROS1* and *MET* genes. Currently, people with NSCLC are tested for these gene variants sequentially – that is, one after another. This application is for a gene panel, which means the laboratory can test for all the gene variants at once. The gene panel approach means that testing doesn't use as much tumour tissue to get a test result and they can get multiple results at the same time from the same tumour sample.

MSAC determined that it made sense for people to have access to this type of gene testing, because using a gene panel makes best use of the tumour tissue available for testing, making it safer (as less biopsies are needed) as well as potentially cheaper and faster than testing one gene at a time. MSAC noted that it is not appropriate to use the gene panel testing for people with squamous cell carcinomas (SCCs) as it is rare for people with SCCs to have gene variants in their *EGFR*, *ALK* and *ROS1* genes. They do sometimes have harmful variants in their *MET* genes, and these people will still be able to access *MET* gene testing.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for small next generation sequencing (NGS) panels for biomarker testing of patients with non-squamous (or histology not otherwise specified) non-small cell lung cancer (NSCLC). MSAC did not support the expansion of the new test item to include patients with squamous NSCLC because it was rare for these patients to harbour the variants covered in the supported NSCLC panels. MSAC considered that the evidence for small gene panel testing demonstrated its superior effectiveness because of 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, MSAC considered there to be acceptable cost effectiveness and financial implications.

MSAC also supported amendments to the existing MBS items for sequential single gene tests.

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

MSAC noted that this application was from the Royal College of Pathologists of Australasia (RCPA) for public funding under the MBS for simultaneous testing of multiple, actionable variants that are responsive to Pharmaceutical Benefits Scheme (PBS)-listed therapies. The test would use small NGS gene panels in patients diagnosed with non-squamous (or histology not otherwise specified) NSCLC.

MSAC has not previously considered any panel testing for NSCLC. MSAC recalled that it has considered individual single gene tests for biomarker assessment in patients with NSCLC, and in November 2017, "MSAC noted that the sequential testing of *EGFR*, *ALK* and *ROS1* yield mutually

exclusive treatment pathways and that sequential testing wastes tissue sample, time and is more expensive than a single panel of tests. MSAC recommended that the Department conduct a cost-utility review of gene panel and/or NGS test options to inform these first-line therapy options. MSAC noted that overall testing may still require more than one gene panel test due to differences in lung cancer gene aberrations as somatic mutations are tested in genomic DNA, whereas gene fusions (such as *ROS1*) are usually tested in cDNA [complementary DNA] prepared from RNA” ([Public Summary Document \[PSD\] 1454:3](#)).

MSAC noted that somatic driver variants can be the primary cause of the cancer proliferating, and that patients who have a specific genetic biomarkers may be eligible for targeted treatment if they have locally advanced or metastatic NSCLC.

MSAC considered that the 2.5% more patients identified with *EGFR* variants under the proposed NGS MBS items would be likely to benefit from existing PBS-subsidised *EGFR* targeted therapies, but considered that this may depend on the variant identified. MSAC also considered that the concordance between NGS and fluorescent in situ hybridisation (FISH) for the detection of *ROS1*, *ALK* and *METex14sk* variants was sufficient to enable NGS to be used to determine eligibility for existing PBS subsidised therapies.

MSAC noted the current PBS listings for *ROS1* and *ALK* require detection to occur by FISH, and that amendments would need to be referred by the Department to the Pharmaceutical Benefits Advisory Committee (PBAC). No changes are required to the existing PBS listings for *EGFR* and *METex14sk* targeted therapies.

MSAC noted that the public stakeholder feedback was strongly supportive of the application, as noted in the pre-MSAC response. In addition, MSAC noted that international guidelines recommend the inclusion of the specified genes as a minimum (given that targeted therapies are available for NSCLC tumours with variants in the specified genes, even if they are not listed on the PBS). Additionally, inclusion of the genes without current PBS listed targeted therapies will future proof the items.

MSAC noted that the testing proposed will be performed by laboratories with genomic testing capability that are accredited by the National Association of Testing Authorities, Australia (NATA). MSAC noted that there were three proposed MBS items:

- AAAA – a small gene panel that includes DNA and RNA analysis (fee of \$1,247)

OR

- BBBB – a small gene panel that includes DNA analysis only (fee of \$682.35)

AND

- CCCC – a small gene panel that includes RNA analysis only, and to be done only if BBBB is negative (fee of \$682.35).

MSAC noted that these proposed items will supersede tests supported under the current sequential gene items over time and provide better use of tumour tissue, and considered that the application demonstrated clinical need.

The current MBS items that will be superseded are:

- 73337 – tumour *EGFR* gene status
- 73341 – tumour FISH for *ALK* status
- 73344 – tumour FISH for *ROS1* (if previous tests for *EGFR* and *ALK* are negative)
- 73436 – tumour *MET* exon 14 skipping gene (*METex14sk*) status.

MSAC agreed with the pre-MSAC response that the testing should be restricted to NSCLC, as squamous cell carcinomas (SCCs) rarely harbour mutations in these genes (except for *MET*ex14sk). MSAC advised that these four MBS items should not be immediately delisted to allow pathology laboratories to transition to the small gene panel testing. It may be suitable to delist these in two years. MSAC also suggested retaining MBS item 73436 for SCC patients. MSAC considered this to be more cost-effective than having SCC patients access NGS testing.

MSAC noted that the proposed item descriptors used the term “episode of disease”, which it determined is not likely to cause confusion for requestors and providers, but suggested that the phrase “once per new diagnosis of a NSCLC” may be more appropriate. This phrase covers synchronous/metachronous disease, and future-proofs for potential neo/adjuvant TKI usage. This phrase would mean that repeat testing for the proposed services would only be indicated in appropriate cases and it would be unnecessary to specify a limit on repeat services either in the item descriptor or the practice notes for the proposed services. However, for symmetry, MSAC advised that if the item descriptors for the proposed services were to be amended this way, the four current MBS items should also be similarly amended to indicate a restriction on repeat services.

MSAC also advised that co-claiming restrictions (per patient episode) should be applied to the proposed services to prevent the simultaneous performance and claiming of tests under multiple methods, and that the equivalent co-claiming restriction (per patient episode) should be applied to the existing sequential gene tests.

MSAC considered that MBS item 73351 (testing for *EGFR* T790M gene status for access to osimertinib under the PBS) should also be on the list of MBS items not able to be co-claimed with the new proposed MBS item numbers. MSAC foreshadowed that MBS item 73351 may eventually be altered to include NGS for other actionable resistance variants, and advised that the Department may want to consider amending the descriptor for item 73351 to “A test of tumour tissue that is derived from a new sample from a patient with locally advanced (Stage IIIb) or metastatic (Stage IV) (NSCLC), who has progressed on or after treatment with a receptor tyrosine kinase inhibitor (TKI) and is to be requested by a specialist or consultant physician, to determine if the requirements relating to gene status for access to a TKI under the [PBS] are fulfilled” as this may help future-proof item 73351 for rebiopsy for other actionable resistance mutations, including T790M, with currently reimbursed or future TKIs, or future antibody–drug conjugates.

MSAC considered it appropriate to include advice about using multiple methodologies (per episode of disease) in a practice note.

MSAC considered it appropriate that the gene panel testing be pathologist determinable.

MSAC considered the proposed fees to be appropriate, but noted that the fees would need to be aligned with the Department’s review on gene panel testing fees.

MSAC recommended the following MBS item descriptors for newly supported items:

AAAA

A nucleic acid-based multi-gene panel test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer requested by, or on behalf of, a specialist or consultant physician, to detect:

- i. variants in at least *EGFR*, *BRAF*, *KRAS* and *MET* exon 14 to determine access to specific therapies relevant to these variants listed on the Pharmaceutical Benefits Scheme (PBS); and
- ii. the fusion status of at least *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK2* and *NTRK3* to determine:
- iii. access to specific therapies relevant to these variants listed on the PBS; or
- iv. if the requirements relating to *EGFR*, *ALK* and *ROS1* status for access immunotherapies listed on the PBS are fulfilled.

Co-claiming of MBS items BBBB, CCCC, 73337, 73341, 73344, 73436 or 73351 is not permitted in the same patient episode.

Fee: \$1,247 Benefit: 75% = \$935.25 85% = \$1,153.8159.0^a

BBBB

A DNA-based multi-gene panel test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer requested by, or on behalf of, a specialist or consultant physician, to detect variants in at least *EGFR*, *BRAF*, *KRAS* and *MET* exon 14 to determine:

- i. access to specific therapies relevant to these variants listed on the Pharmaceutical Benefits Scheme (PBS); or
- ii. if the requirements relating to *EGFR* status for access to immunotherapies listed on the PBS are fulfilled.

Co-claiming of MBS item AAAA, 73337, 73436 or 73351 is not permitted in the same patient episode.

Fee: \$682.35 Benefit: 75% = \$511.75 85% = \$589.15^a

CCCC

A nucleic acid-based multi-gene panel test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer and with documented absence of activating variants of the *EGFR* gene, *KRAS*, *BRAF* and *MET* exon14, requested by, or on behalf of, a specialist or consultant physician, to determine:

- i. the fusion status of at least *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK2*, and *NTRK3* to determine access to specific therapies relevant to these variants listed on the Pharmaceutical Benefits Scheme (PBS) are fulfilled; or
- ii. if the requirements relating to *ALK* and *ROS1* status for access to immunotherapies listed on the PBS are fulfilled.

Co-claiming of MBS items AAAA, 73341, 73344 or 73351 is not permitted in the same patient episode.

Fee: \$682.35 Benefit: 75% = \$511.75 85% = \$589.15^a

a Reflects the 1 November 2022 Greatest Permissible Gap (GPG) of \$93.20. All out-of-hospital Medicare services which have an MBS fee of \$621.50 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).

MSAC recommended the following amendments to item descriptors for existing items:

73337

A test of tumour tissue from a patient diagnosed with a new diagnosis of non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to determine:

- a) if requirements relating to epidermal growth factor receptor (EGFR) gene status ~~for access to an EGFR tyrosine kinase inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled; or~~
- b) ~~if the requirements relating to EGFR status~~ for access to an immunotherapy listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Co-claiming of MBS items AAAA or BBBB is not permitted in the same patient episode.

Fee: \$397.35 Benefit: 75% = \$298.05 85% = \$337.75

73341

Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with a new diagnosis of locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (ALK) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score > 0, and with documented absence of activating mutations of the epidermal growth factor receptor (EGFR) gene, requested by a specialist or consultant physician, to determine:-

- a) if requirements relating to ALK gene rearrangement status ~~for access to an anaplastic lymphoma kinase inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled;~~ or
- b) ~~if requirements relating to~~ ALK status for access to an immunotherapy listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Co-claiming of MBS items AAAA or CCCC is not permitted in the same patient episode.

Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00

73344

Fluorescence in situ hybridization (FISH) test of tumour tissue from a patient with a new diagnosis of locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of ROS proto-oncogene 1 (ROS1) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+; and with documented absence of both activating mutations of the epidermal growth factor receptor (EGFR) gene and anaplastic lymphoma kinase (ALK) immunoreactivity by IHC, requested by a specialist or consultant physician, to determine:

- a) if requirements relating to ROS1 gene arrangement status ~~for access to crizotinib or entrectinib a relevant under the Pharmaceutical Benefits Scheme (PBS) are fulfilled;~~ or
- b) ~~if requirements relating to~~ ROS1 status for access to an immunotherapy listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Co-claiming of MBS items AAAA or CCCC is not permitted in the same patient episode.

Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00

73436

A test of tumour tissue from a patient diagnosed with a new diagnosis of locally advanced or metastatic non-small cell lung cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to MET proto-oncogene, receptor tyrosine kinase (MET) exon 14 skipping alterations (METex14sk) status for access to ~~tepotinib an immunotherapy listed are fulfilled~~ under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Co-claiming of MBS items AAAA or BBBB is not permitted in the same patient episode.

Fee: \$397.35 Benefit: 75% = \$298.05 85% = \$337.75

MSAC recommended the following practice note to apply to the three new (AAAA, BBBB and CCCC) and four existing (73337, 73341, 73344, 73436) MBS items.

PN.X.X

Repeat testing for non-small cell lung cancer (NSCLC) by multiple methodologies:

Prior to requesting or performing these tests, the requesting practitioner or pathologist should consider if the patient has already received equivalent testing under the same or another methodology in the same new diagnosis of non-small cell lung cancer (NSCLC).

Repeat testing by multiple methods in the same new diagnosis of NSCLC should only be performed if it is clinically relevant.

Items 73337, 73341, 73344 and 73436 support sequential single-gene testing for biomarkers in patients with NSCLC.

Items AAAA supports use of one next generation sequencing (NGS) panel for testing of all biomarkers supported under items 73337, 73341, 73344 and 73436.

Items BBBB and CCCC supports sequential use of two NGS panels for testing of all biomarkers supported under 73337 and 73436, and 73341 and 73344 respectively.

MSAC noted that the two proposed clinical management algorithms are for simultaneous DNA and RNA testing, or sequential DNA and RNA testing. MSAC noted that the comparator was sequential testing using different methods (DNA, RNA, FISH and IHC) and considered these to be appropriate, both options would result in more simplified testing compared to the current clinical management algorithms.

MSAC noted that the clinical evidence was derived from a systematic review that identified 49 studies addressing health outcomes (24 studies), test performance (40 studies), concordance of NGS with single-gene tests (30 studies) and change of management (8 studies). One study, (with moderate to high risk of bias) demonstrated that NGS-selection of patients is superior to immunohistochemistry or FISH for *ALK* testing.¹ The proportion of samples successfully tested (based on having sufficient tissue/DNA/RNA for testing) was assessed in only one between-patient study (Steeghs et al²), although this was large ($n = 4,040$) and had low-to-moderate risk of bias. However, MSAC noted that this study may not be directly applicable, as its healthcare setting (in the Netherlands) used a combination of DNA NGS with fusion testing performed by IHC or FISH or RNA NGS rather than just DNA and RNA NGS.

MSAC noted that no studies directly compared the safety of NGS testing with sequential single-gene testing. However, the evidence supported the claim that NGS had a higher proportion of samples being successfully tested (i.e. making more efficient use of the available tissue to get a test result) than sequential single-gene testing, which should correspond to a lower rate of rebiopsy. Steeghs et al. (2022) reported that NGS methods were successful in 97.2% of cases, whereas non-NGS methods were successful in 94.6% of cases.

MSAC noted the below summary of concordance data between NGS and single-gene testing. MSAC considered that an outstanding issue was the lack of documented improved outcomes with testing.

¹ Lin C, et al. 2019, 'Comparison of *ALK* detection by FISH, IHC and NGS to predict benefit from crizotinib in advanced non-small-cell lung cancer', *Lung Cancer*, vol. 131, May, pp. 62-68

² Steeghs E, et al. (2022). Mutation-tailored treatment selection in non-small cell lung cancer patients in daily clinical practice. *Lung Cancer*, vol. 167, May, pp. 87-97.

Table 1 ES: Summary of concordance data between NGS and single-gene testing

Gene	Evidence base	PPA (95%CI)	NPA (95%CI)	Prevalence	Per 1000 successfully tested (95%CI)				PPV (95%CI)	NPV (95%CI)
					NGS+ /SG+	NGS+ /SG-	NGS- /SG+	NGS- /SG-		
<i>EGFR</i>	n=2611 k=22	0.98 (0.95, 0.99)	0.97 (0.95, 0.99)	15% ^a	147 (143, 149)	25 (8, 42)	3 (1, 7)	825 (808, 842)	0.85	1.00
<i>ALK</i>	n=1464 k=11	0.92 (0.77, 0.97)	0.99 (0.93, 1.00)	3% ^b	28 (23, 29)	10 (0, 68)	2 (1, 7)	960 (902, 97)	0.74	1.00
<i>ROS1</i>	n=830 k=6	0.86 (0.63, 0.96)	1.00 (0.99, 1.00)	1.61% ^c	14 (10, 15)	0 (0, 10)	2 (1, 6)	984 (974, 984)	1.00	1.00
<i>MET</i> ex14sk	n=99 k=1	0.98 (0.89, 1.00)	1.00 (0.93, 1.00)	3.6% ^d	35 (32, 36)	0 (0, 69)	1 (0, 4)	964 (895, 964)	1.00	1.00
Total					224	35	8	733		

ALK = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; *MET* = mesenchymal-epithelial transition; NGS = next generation sequencing; NPA = negative percent agreement; NPV= negative predictive value; PPA = positive percent agreement; PPV = positive predictive value; *ROS1* = ROS proto-oncogene 1; SG = single-gene testing

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. MSAC noted that, after stepped economic analysis, the incremental cost-effectiveness ratio (ICER) was \$7,496 per additional patient eligible for targeted therapy. The ICER was highly sensitive to:

- changes in the estimate of patients with advanced disease
- *EGFR* negative per cent agreement values
- RNA panel use (item CCCC).

MSAC noted that the ICER was moderately sensitive to test success and rebiopsy uptake.

MSAC noted that the modelling used 30% in-hospital and 70% outpatient split, which it considered to be appropriate.

MSAC noted that the DCAR estimated a net financial impact to the MBS of approximately \$1.47 million in year 1 (2023) to \$2.28 million in year 6 (2028), noting the true financial impact is expected to be marginally higher, as it was calculated by the DCAR using Greatest Permissible Gap (GPG) of \$87.90 that applied from 1 November 2021 to 31 October 2022.

MSAC noted that if PBAC does not support amendments to the existing PBS listings for *ALK* and *ROS1* targeted therapies, the estimated net financial impact to the MBS will increase by approximately \$0.1 million in each year, as confirmatory FISH testing will be required to access PBS-listed therapies.

MSAC noted that as a result of the identification of an [REDACTED] patients eligible for targeted therapies, there would also be an [REDACTED] to the PBS of \$ [REDACTED] over the next six years.

Overall, 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.

4. Background

MSAC has not previously considered any panel testing for NSCLC.

A similar assessment for a somatic tumour panel test (that was not histology-specific) was initiated in 2018 (MSAC assessment 1495), but was withdrawn prior to being considered by MSAC, as no single somatic tumour panel test could appropriately assess epidermal growth factor receptor (*EGFR*), ALK receptor tyrosine kinase (*ALK*) and ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*) variants at the time. In the same year, an application (MSAC assessment 1634) was also made by Roche Diagnostics for MBS listing of a comprehensive gene panel of over 300 genes for use in squamous and non-squamous NSCLC, which was revised in 2020 to focus on non-squamous NSCLC. During the PICO development, the applicant for 1634 nominated the application would proceed as an ADAR for consideration at an MSAC meeting in late 2022. However, in May 2022, the applicant notified the Department that it would be delaying the submission of its ADAR.

MSAC has considered individual single gene tests for biomarker assessment in patients with NSCLC, and in November 2017, *“MSAC noted that the sequential testing of EGFR, ALK and ROS1 yield mutually exclusive treatment pathways and that sequential testing wastes tissue sample, time and is more expensive than a single panel of tests. MSAC recommended that the Department conduct a cost-utility review of gene panel and/or next generation sequencing (NGS) test options to inform these first-line therapy options”*. *“MSAC advised that any MBS funding should be based on a gene panel or NGS test of equivalent or better analytical performance to sequential IHC and FISH testing and assurance that the average gene panel or NGS test is no more costly than the average cost of the sequential testing that it would replace. MSAC noted that overall testing may still require more than one gene panel test due to differences in lung cancer gene aberrations as somatic mutations are tested in genomic DNA, whereas gene fusions (such as ROS1) are usually tested in cDNA [complementary DNA] prepared from RNA.”* ([Public Summary Document, ADAR 1454](#), November 2017, p3).

A summary of how this DCAR has addressed the suggestions by MSAC is shown in Table 1.

Table 1 Summary of key matters of concern from MSAC 1454 PSD, November 2017, p3

Component	Matter of concern	How the current assessment report addresses it
Overarching DCAR	MSAC recommended that the Department conduct a cost-utility review of gene panel and/or next generation sequencing (NGS) test options to inform these first-line therapy option.	Addressed. Current DCAR assessing small NGS panel.
Intervention	MSAC noted that overall testing may still require more than one gene panel test due to differences in lung cancer gene aberrations as somatic mutations are tested in genomic DNA, whereas gene fusions (such as <i>ROS1</i>) are usually tested in complementary DNA prepared from RNA.	Addressed. Intervention proposed as both DNA and RNA testing, or sequential DNA then RNA testing.
Test performance	Any MBS funding should be based on a gene panel or NGS test of equivalent or better analytical performance to sequential IHC and FISH testing.	Addressed. NGS has superior or equivalent analytical performance compared to single-gene assays or IHC and FISH testing.
Cost-minimisation	The average gene panel or NGS test is no more costly than the average cost of the sequential testing that it would replace.	At the proposed items fees, small gene panel testing is associated with additional costs. This may be reasonable if the claim of superior effectiveness is accepted.

DCAR = Department Contracted Assessment Report; DNA = deoxyribonucleic acid; FISH = fluorescence *in situ* hybridisation; IHC = immunohistochemistry; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; NGS = next generation sequencing; PSD = Public Summary Document; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase; RNA = ribonucleic acid.

5. Prerequisites to implementation of any funding advice

Small DNA/RNA or DNA and RNA NGS panel testing would occur in a National Association of Testing Authorities (NATA) accredited laboratory in accordance with National Pathology Accreditation Advisory Council (NPAAC) guidelines: '[Requirements for human medical genome testing utilising massively parallel sequencing technologies \(First Edition 2017\)](#)'.

Currently, there are no NGS assays approved by the Therapeutic Goods Administration (TGA) for the purposes of detecting biomarkers for targeted treatment of patients with NSCLC. There are several NGS assays available in Australia for 'Research Use Only' (RUO), and local laboratories will be able to purchase RUO products and develop an *in vitro* test medical device approved by the National Association of Testing Authorities (NATA) as per the framework in '[Requirements for the development and use of in-house *in vitro* diagnostic medical devices \(IVDs\) \(Fourth Edition 2018\)](#)'.

Currently, the PBS restrictions for most of the drugs targeting *ALK* or *ROS1* gene rearrangements (all except second-line lorlatinib) specify the method of determining the variants and the threshold separating a positive result from a negative result (i.e., patients must have evidence of an *ALK* gene rearrangement or *ROS1* gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence *in situ* hybridisation (FISH) testing). If the proposed items for small DNA ± RNA NGS panels are listed on the MBS, coordinated amendments to the restrictions listed on the PBS would be required to allow for biomarkers to be detected using either FISH (with the current restriction to ≥15% of positive cells) or NGS (without the same threshold) in the criteria for crizotinib, ceritinib, alectinib, and entrectinib.

6. Proposal for public funding

The proposal is for up to three new MBS items to be listed: one for a nucleic acid-based test of both DNA and RNA for simultaneous testing, and two additional items for separate DNA and RNA testing (as not many laboratories currently have the capacity to perform simultaneous testing). Consistent with current items for *EGFR* testing, IHC testing for *ALK* and *ROS1*, and FISH testing for *ALK* and *ROS1*, the items are proposed to be pathologist-determinable.

The proposed fees are based on the cost of delivering the tests, including extraction, pathologist assessment, quality control, curation and reporting ([MSAC application 1721](#)).

Table 2 Applicant proposed MBS items with suggested modifications proposed by HTA Group and/or the Department for ESC consideration

Category 6 – Genetics P7	
AAAA	<p>A nucleic acid-based multi-gene panel test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to detect:</p> <ol style="list-style-type: none"> variants in at least <i>EGFR</i>, <i>BRAF</i>, <i>KRAS</i> and <i>MET</i> exon 14 to determine access to specific therapies listed on the Pharmaceutical Benefits Scheme (PBS); and the fusion status of at least <i>ALK</i>, <i>ROS1</i>, <i>RET</i>, and <i>NTRK</i> to determine access to specific therapies listed on the PBS; or if the requirements relating to <i>EGFR</i>, <i>ALK</i> and <i>ROS1</i> status for access to a PD-(L)1 immunotherapy pembrolizumab under the PBS are fulfilled. <p>Maximum one test per episode of disease This item cannot be claimed in addition to MBS items BBBB, CCCC, 73337, 73341, 73344, or MBS item for <i>MET</i>ex14sk testing</p> <p>Fee: \$1,247 Benefit: 75% = \$935.25 85% = \$1,159.10^a</p>
BBBB	<p>A DNA-based multi-gene panel test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to detect:</p> <ol style="list-style-type: none"> variants in at least <i>EGFR</i>, <i>BRAF</i>, <i>KRAS</i> and <i>MET</i> exon 14 to determine access to specific therapies listed on the Pharmaceutical Benefits Scheme (PBS); or if the requirements relating to <i>EGFR</i> status for access to a PD-(L)1 immunotherapy pembrolizumab under the PBS are fulfilled. <p>Maximum one test per episode of disease This item cannot be claimed in addition to MBS item AAAA, 73337, or MBS item for <i>MET</i>ex14sk testing</p> <p>Fee: \$682.35 Benefit: 75% = \$511.75 85% = \$594.45^a</p>
CCCC	<p>A nucleic acid-based multi-gene panel test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, and with documented absence of activating mutations variants of the <i>EGFR</i> gene, <i>KRAS</i>, <i>BRAF</i> and <i>MET</i> exon14, requested by, or on behalf of, a specialist or consultant physician, to detect:</p> <ol style="list-style-type: none"> the fusion status of at least <i>ALK</i>, <i>ROS1</i>, <i>RET</i>, and <i>NTRK</i> to determine access to specific therapies listed on the Pharmaceutical Benefits Scheme (PBS) are fulfilled; or if the requirements relating to <i>ALK</i> and <i>ROS1</i> status for access to a PD-(L)1 immunotherapy pembrolizumab under the PBS are fulfilled. <p>Maximum one test per episode of disease This item can only be claimed if the result from MBS item number BBBB is negative, and cannot be claimed in addition to MBS items AAAA, 73341, 73344</p> <p>Fee: \$682.35 Benefit: 75% = \$511.75 85% = \$594.45^a</p>

^a Reflects the 1 November 2021 Greatest Permissible Gap (GPG) of \$87.90. All out-of-hospital Medicare services which have an MBS fee of \$586.20 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). Suggested changes to the MBS items are shown in red and strikethrough text.

The proposal is that item CCCC (for RNA testing) would only be used if targetable biomarkers are not already detected by item BBBB (DNA testing). Although additional genes may be tested as part of the panels (as those listed are currently considered the minimum), a variant identified in other genes on the DNA panel (for which there is not a PBS-listed treatment available) is not intended to prohibit further testing of the RNA.

Note, the proposed items include testing of genes which currently do not have PBS-listed specific therapies for NSCLC (i.e. *KRAS*, *BRAF*, *MET*exon14, *RET* and *NTRK1*, *NTRK2* and *NTRK3*), although *MET*ex14sk has a PBAC-recommended specific therapy, which is not yet PBS-listed. The applicants justified the additional genes by referencing international guidelines, which recommend the inclusion of the specified genes as a minimum (given targeted therapies are available for NSCLC tumours with variants in the specified genes, even if they are not PBS-listed). This should future-proof the items in case the targeted therapies become PBS-listed in the near future. Concurrent variants in the listed genes are rare, so identifying pathogenic variants in the *KRAS*, *BRAF*, *RET* or the three *NTRK* genes is highly likely to rule out the presence of rearrangements in *ALK* or *ROS1* genes. The additional genes are therefore reasonable to include, although it may result in a very small number of patients with *ALK* or *ROS1* variants in their tumour not being identified, and consequently missing out on receiving an appropriate targeted therapy.

The proposal to refer to a PD-(L)1 immunotherapy rather than pembrolizumab reflects the fact that the PBS restriction for NSCLC of several of these medicines require that the “condition must not have evidence of an activating epidermal growth factor receptor (*EGFR*) gene or an *ALK* receptor tyrosine kinase (*ALK*) gene rearrangement in tumour”. If MSAC supports this suggestion, then the related changes required to existing MBS items 73337, 73341 and 73344 would align with the equivalent changes to these existing MBS items that have already been supported by MSAC under MSAC Application 1642.

Sensitivity analyses were performed to assess the impact of allowing patients with *KRAS* or *BRAF* variants to undergo RNA testing.

7. Population

The target population are those diagnosed with non-squamous or not otherwise specified (NOS) NSCLC. It is estimated that in 2021, there were 11,738 newly diagnosed cases of NSCLC in Australia.

There are a number of different somatic variants which are important to identify in NSCLC tumours, as they may be the primary cause of the cancer growing and dividing. For many variants in NSCLC tumours, there are targeted treatments which have been found effective, and identification of the biomarker can therefore allow optimal treatment of the tumour. The targeted treatments currently listed on the PBS are:

- erlotinib, gefitinib, afatinib, osimertinib (for *EGFR* activating variants),
- osimertinib (for *EGFR* T790m variant after prior *EGFR* targeted treatment),
- crizotinib, ceritinib, alectinib, brigatinib, lorlatinib (for *ALK* rearrangements),
- crizotinib and entrectinib (for *ROS1* rearrangements), and
- PD-(L)1 immunotherapies (for those with an absence of activating *EGFR* variants, *ALK* rearrangements or *ROS1* rearrangements).

Tepotinib has also been recommended for those with *MET*ex14sk alterations.

Currently, the testing for the relevant biomarkers is done in a sequential manner, with *EGFR* variants the first to be tested (testing pathologist-determinable, and *EGFR* testing may occur as soon as NSCLC which is non-squamous or NOS is diagnosed). As small NGS gene panels are expected to replace the use of single gene testing, the projected number of patients who would use the proposed intervention can be estimated based on historical use of *EGFR* testing under MBS item 73337. A survey performed for the purposes of [PICO confirmation 1669](#) reported that most laboratories are already using small DNA panels. If the proposed separate DNA and RNA panels are added to the MBS, then the small DNA panel item is likely to be able to be used by most laboratories from the time of listing (Table 4). However, capacity to perform small RNA panels is more restricted, and in the near future, laboratories may either transfer the tissue to another laboratory for RNA testing or continue to use IHC and FISH for the assessment of *ALK* and *ROS1*. The applicants have also stated that some patients will have insufficient tumour tissue available for RNA to be extracted, so 5-10% of cases may continue to be tested using FISH rather than an NGS panel.

Prior testing, and projections of use only consider testing in patients with non-squamous (or not otherwise specified) histology, and do not consider the utilisation if patients with squamous NSCLC are also tested. This is estimated to increase the projections by 15%. (Note that Tables 3 and 4 report utilisation and projected utilisation by calendar year).

Table 3 Use of MBS item 73337, 2015–2021*

	2015	2016	2017	2018	2019	2020	2021
No. services	3,368	3,419	3,863	4,147	4,603	4,697	4,854

Source: Services Australia

Table 4 Projected use of small gene panel testing (assuming 100% market share)

	2023	2024	2025	2026	2027	2028
Projected use of item 73337	5,521	5,797	6,074	6,351	6,628	6,905

If a patient has a biomarker identified by the small NGS gene panel (or the comparator), they may then be eligible for targeted treatment if they have locally advanced (stage IIIB) or metastatic (stage IV) NSCLC at the point of diagnosis, or once they progress to having locally advanced or metastatic disease.

If patients progress while on treatment, they may be suspected of having developed intolerance to treatment due to resistance-variants and may be tested for the *EGFR* T790M resistance variant. The use of this test is not expected to alter with the introduction of the small NGS panels.

The studies in the systematic review were included if at least 80% of the patients had non-squamous NSCLC (i.e. studies with a small proportion of squamous NSCLC were allowed as it was considered they would not influence the results significantly).

8. Comparator

The comparator to (one or two) small NGS panels is the use of sequential testing of biomarkers for targeted therapies for NSCLC using items currently available on the MBS (or in the near future). Specifically, this is:

- Testing of *EGFR* activating variant status (MBS item 73337)
- Immunohistochemistry (IHC) testing as triage ALK testing and triage ROS1 testing (most likely included under MBS item 72846 at the time of initial diagnosis)
- Testing of *ALK* gene rearrangement status by FISH (MBS item 73341)
- Testing of *ROS1* gene rearrangement status by FISH (MBS item 73344)
- Testing of *METex14* skipping alterations (recommended by MSAC)

At the point of diagnosis, patients are tested for *EGFR* activating variants using a single gene test and with IHC for ALK and ROS1 protein expression. MSAC has recommended that testing for *METex14* skipping (*METex14sk*) alterations be performed without the absence of other NSCLC biomarkers being a pre-requisite (Public Summary Document, ADAR 1660, p1). Although *METex14sk* testing is limited to patients with locally advanced or metastatic disease, the majority of patients meet this criteria at the point of diagnosis, so are assumed to be tested for *METex14sk* at the point of diagnosis.

If the patient's tumour is *EGFR* activating variant negative, but positive or equivocal on ALK IHC triage testing (staining intensity score >0), they may undergo confirmatory *ALK* gene rearrangement testing using FISH if/when they have locally advanced or metastatic disease.

Likewise, if the patient's tumour is *EGFR* variant negative, but positive or equivocal on ROS1 IHC triage testing (staining intensity score of 2+ or 3+), they may undergo confirmatory *ROS1* gene rearrangement testing using FISH if/when they have locally advanced or metastatic disease.

If patients do not have locally advanced or metastatic disease at the time of diagnosis, then a block retrieval item (MBS item 72860) may be required if referral to an outside laboratory is required for the FISH testing.

The small NGS panels are expected to replace all of these separate genetic tests, and will also include the three *NTRK* gene tests which are currently not MBS-reimbursed. Other tests which co-occur at the point of diagnosis (but will not be affected by the introduction of NGS), are IHC to determine programmed death-ligand 1 (PD-L1) levels (noting that the PBS restriction for pembrolizumab in NSCLC is now agnostic for PD-L1 status).

9. Summary of public consultation input

Consultation input was received from seven (7) organisations. No feedback was received from consumer organisations or individual consumers or carers for this application. The feedback was strongly supportive of public funding of small gene panel testing for non-small cell lung carcinoma. The organisations that submitted input were:

- Public Pathology Australia (PPA)
- Human Genetics Society of Australasia (HGSA)
- Roche Products Pty Ltd and Roche Diagnostics Australia
- Australian Genomics Health Alliance (AGHA)
- InGeNA
- Janssen-Cilag Pty Ltd
- The Thoracic Oncology Group of Australasia (TOGA)

Key benefits of the proposed testing were identified as:

- *“Allowing contemporaneous testing on a single platform will have a dual advantage of making more tissue available for the single test and return results for selection of optimal therapy in a short timeframe.”*
- *“MBS funding of a panel-based service positions molecular pathology laboratories to support evolution of molecular testing to keep pace with new therapy developments.”*
- Funding the test will align with current clinical practice for testing in these patients.
- Funding the testing will support equity of access for patients.
- It may reduce the need for re-biopsy.
- Funding the testing will standardise molecular testing in lung cancer which will improve patient outcomes.
- The test will allow for faster and more comprehensive genomic testing which may facilitate earlier access to targeted therapies for patients. One organisation stated that up to 75% of patients present with advanced stage of the disease and do not undergo surgery.
- It may ensure that patients don't receive treatments they don't need, which reduces the cost to the health system.

Potential disadvantages of the proposed genetic testing were identified as:

- *“Due to the limited size, small gene panels may preclude patients with rare alterations from receiving targeted therapy and potentially improving their health outcomes.”*
- The knowledge surrounding biomarkers and targets for testing is growing and the small gene panel may not be sufficient to guide best clinical care in future.

10. Characteristics of the evidence base

A total of 49 studies were identified from the systematic review, assessing the direct from test to health outcomes evidence, test performance, and change in management. The majority of the evidence was on test performance (k=40), with 30 studies reporting on the concordance of NGS with single gene tests. Conclusions on the concordance of the tests could therefore be made with high certainty. The proportion of samples successfully tested (based on having sufficient tissue/DNA/RNA for testing) was assessed in only one between-patient study, although this was large (n=4040) and had low to moderate risk of bias. However, the evidence may not be directly applicable, as the healthcare setting in the Netherlands used a combination of DNA NGS with fusion testing performed by IHC or FISH or RNA NGS rather than just DNA and RNA NGS.

Change in management data (predictive yield and uptake of rebiopsy) and test-to-health outcomes data (clinical utility) were very limited. However, the last step of linked evidence (assessing the impact of the change of management) was supplemented by targeted (non-systematic) searches, which provided reasonable certainty in regards to the harms associated with rebiopsy, and low certainty evidence that the additional targetable variants identified by NGS are likely to respond to targeted therapies. The economic analysis incorporates the test performance data (concordance and proportion of tests performed successfully) and proportion of samples rebiopsied.

Although the target population was non-squamous NSCLC (or NOS), studies were included if no more than 15% of the included samples were squamous. Where data could be extracted separately for patients with non-squamous tumours, this was done (such as for some of the key evidence provided by Steeghs et al. (2022)), but the majority of studies did not provide subgroup analyses.

Table 5 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Accuracy and performance of the test (cross-sectional accuracy)	Evidence that NGS is highly concordant with single-gene testing, and detects more extra cases than it misses Evidence that NGS has a higher proportion of samples successfully tested (better use of tumour tissue)	☒ k=30 n=4081 ☒ k=1 n=4040	Low to moderate risk of bias (QUADAS 2)
Change in patient management	Evidence that shows that use of NGS influences the treatments given in those with discordant results. Evidence that shows that some patients with insufficient tissue are rebiopsied	☒ k=6 n=99 ☒ k=2 n=225	Low to moderate risk of bias (QUADAS 2) (However, very small heterogeneous studies)
Health outcomes	Evidence that extra cases detected by NGS are likely to respond to TKIs Evidence that avoiding rebiopsies is safer than undergoing rebiopsy	☒ k=8 n=2921 ☒ k=16 n=2326	Moderate risk of bias (NHLBI for case series, AMSTAR 2 for SRs)
Predictive effect (treatment effect variation)	Evidence that NGS-selection of patients for <i>ALK</i> TKIs is superior to IHC- or FISH-selection for <i>ALK</i> TKIs	☒ k=1 n=50	Moderate to high risk (QUIPS checklist)

ALK = ALK receptor tyrosine kinase; AMSTAR 2 = Assessing the Methodological Quality of Systematic Reviews; FISH = fluorescent *in situ* hybridisation; IHC = immunohistochemistry; k=number of studies, n=number of patients; NGS = next generation sequencing; QUADAS 2 = Quality assessment tool for diagnostic accuracy studies; QUIPS = Quality of Prognostic Studies tool; SRs = systematic reviews; TKI = tyrosine kinase inhibitor (therapy)

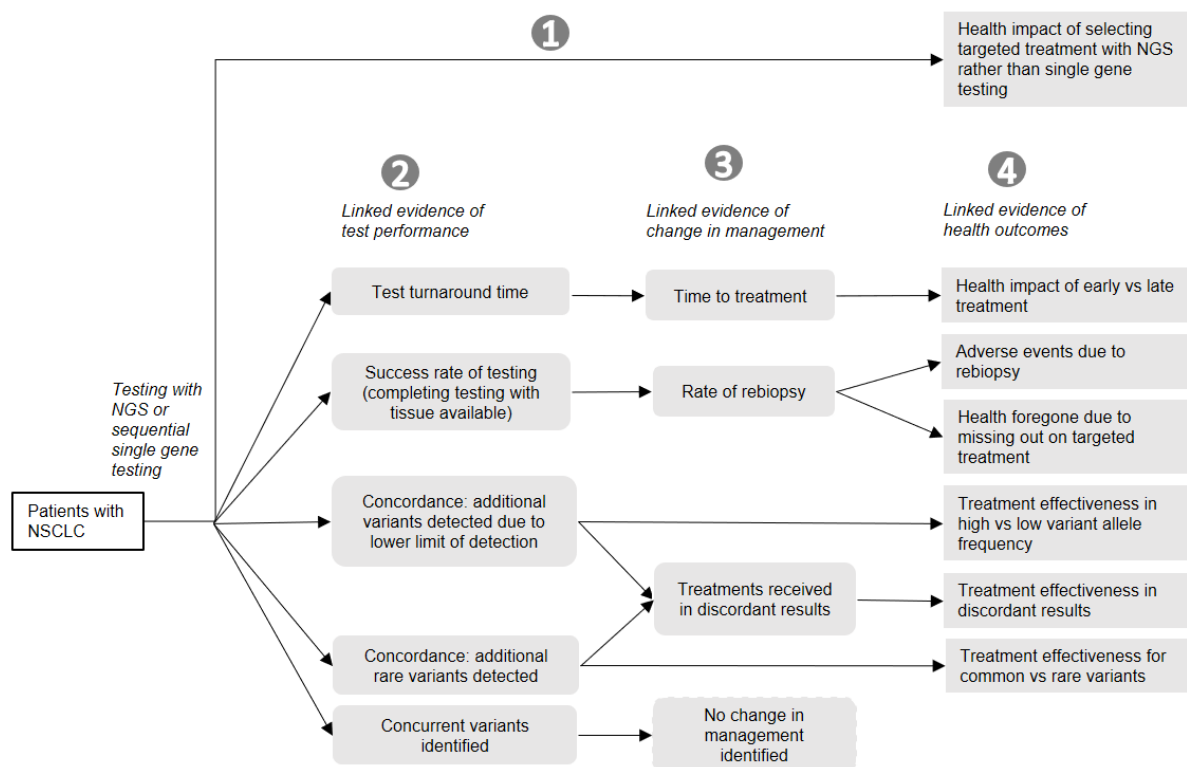


Figure 1 Assessment framework for small DNA/RNA NGS panel vs sequential single gene testing in patients with non-squamous (or NOS) NSCLC

Figure notes: 1: direct from test to health outcomes evidence; 2: test performance; 3: change in treatment/management; 4: influence of the change in management on health outcomes

11. Comparative safety

No studies directly compared the safety of NGS testing with sequential single-gene testing. However, the evidence supported the claim that NGS had a higher proportion of samples being successfully tested (i.e. making more efficient use of the available tissue to get a test result) than sequential single-gene testing, which should correspond to a lower rate of rebiopsy. A single between-patient comparison (Steeghs et al (2022)) was identified in a retrospective cohort study with a low to moderate risk of bias (a further three studies provided within-patient comparisons, but these were considered to not be as informative, as the volume of tissue used for one method of testing would influence the volume of tissue remaining for the alternative method of testing, and the ordering of testing would highly bias the proportion of samples successfully tested). Steeghs et al. (2022) reported that NGS methods were successful in 97.2% of cases, whereas non-NGS methods were successful in 94.6% of cases (Figure 2).

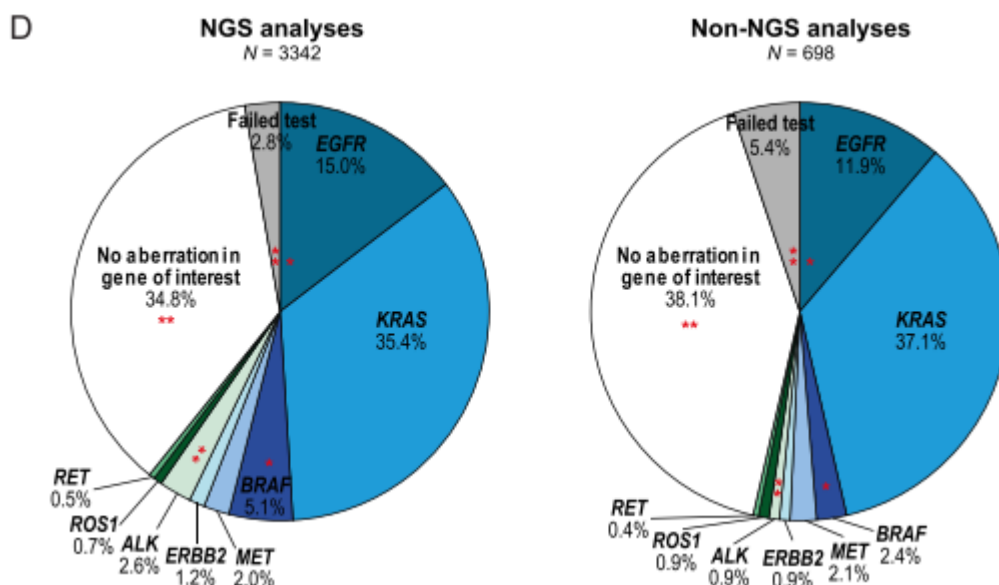


Figure 2 Comparison of pathogenic variants identified by NGS vs non-NGS methods (Sanger sequencing, HRM, MassARRAY, Pyrosequencing, Idylla, Cobas, ddPCR, FISH, IHC and/or RNA-based sequencing) in patients with adenocarcinoma.

Source: Steeghs et al, 2022, p91. Reproduced with permission under Creative Common CC-BY license.

ALK = ALK receptor tyrosine kinase; BRAF = B-Raf proto-oncogene, serine/threonine kinase; ddPCR = digital droplet polymerase chain reaction; EGFR = epidermal growth factor receptor; ERBB2 = erb-b2 receptor tyrosine kinase 2; FISH = fluorescent *in situ* hybridisation; HRM = high resolution melting; IHC = immunohistochemistry; KRAS = KRAS proto-oncogene, GTPase; MET = mesenchymal-epithelial transition; NGS = next generation sequencing; RET = ret proto-oncogene; RNA = ribonucleic acid; ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase; If multiple variants were identified in one patient, only the first variant was included in the pie chart (so that the sum = 100%), **p<0.01, *p<0.05

The relationship between insufficient tissue for testing, or test failure due to insufficient DNA or RNA and subsequent rebiopsy is uncertain, as some international guidelines now recommend the use of liquid biopsy (i.e., using a blood sample) when tumour tissue is insufficient, rather than performing a second biopsy of tumour tissue/cytology. Two case series reported that 13% and 43% of patients with insufficient tissue for NGS or testing EGFR and ALK (by an unspecified method) had a rebiopsy performed, with the remainder either having plasma NGS, or not having their tumour further biomarker-tested^{3,4}. No Australian guidelines were able to be identified on the role of rebiopsy versus liquid biopsies in the absence of sufficient tissue from the initial biopsy. However, these case series data are unlikely to be relevant to the current Australian setting, as the PBS restrictions for targeted therapies in NSCLC require the biomarkers to be identified in tumour tissue. A higher proportion of failed tests are therefore likely to proceed to rebiopsy than reported in these case series.

With each rebiopsy, there is a risk of additional adverse events. A systematic review of 16 studies in patients with NSCLC undergoing percutaneous transthoracic needle biopsies (PTNBs) or rebiopsies for biomarker testing, reported that the risk of any adverse event was 17% (95%CI 12%, 23%). The most common complication was pneumothorax (collapsed lung), with a pooled

³ Gutierrez ME, et al. (2017). Genomic Profiling of Advanced Non-Small Cell Lung Cancer in Community Settings: Gaps and Opportunities. *Clin Lung Cancer*, vol. 18, no. 6, Nov, pp. 651-659.

⁴ Li, W, et al. (2021), 'Metastatic NSCLCs With Limited Tissues: How to Effectively Identify Driver Alterations to Guide Targeted Therapy in Chinese Patients', *JTO Clin Res Rep*, vol. 2, no. 5, May, p. 100167.

incidence of 9.2% (95%CI 4.0%, 15.7%)⁵. Severe adverse events (pneumothorax requiring chest tube, massive haemoptysis, air embolism and death) occurred in less than 1%. Although the authors of meta-analysis reported that PTNBs were safe, it is clear that a reduction in the need for rebiopsy would reduce the risk of adverse events associated with biopsies.

Linked evidence (of proportion of samples successfully tested, the frequency of rebiopsy, and risk of adverse events due to rebiopsy) therefore supported the claim that NGS has superior safety to sequential single-gene testing. The key uncertainties are the extent to which patients in Australia currently undergo rebiopsy when the volume of tissue available is insufficient, and whether practice in Australia will change in the near future to incorporate liquid biopsy as an alternative to tissue rebiopsy.

12. Comparative effectiveness

The claims made by the applicant was that NGS is superior to sequential single-gene testing, as it makes more efficient use of tumour tissue. This results in a higher proportion of patients being successfully tested, having biomarkers identified, and able to receive targeted treatment (which should result in superior health outcomes). NGS may also detect concurrent variants, which is unlikely with sequential single-gene testing as testing is halted once a targetable biomarker is identified (concurrent variants may influence treatment or provide prognostic information). NGS may also provide faster results than sequential single-gene testing (resulting in faster access to targeted treatment and superior health outcomes). The evidence addressing these claims was examined.

As outlined in the safety section, a single between-patient study was identified which provided the proportion of samples successfully tested, favouring NGS over sequential single-gene testing (97.2% vs 94.6%).

In order to test how concordant NGS and sequential single-gene testing are, within-patient studies were required, which provide data to compile a 2x2 table. A total of 30 relevant studies were identified in patients with NSCLC, with results separated per gene (rather than per person or per variant). The positive percent agreement (akin to the concept of sensitivity) and negative percent agreement (akin to the concept of specificity) were meta-analysed (where possible). These data were then transformed back into 2x2 data (per 1000 patients), using prevalence figures appropriate to Australia. The summary of these results is shown in Table 6.

In cases successfully tested by both testing strategies, NGS and sequential single-gene testing were highly concordant, with 95.7% of cases receiving the same test result from both strategies (22.4% with a biomarker, and 73.3% without biomarkers). Overall, NGS was estimated to result in an additional 35 cases per 1000 tested with variants identified which would have been missed by single-gene testing, with 8 cases per 1000 having a biomarker missed by NGS, which would have been detected by single-gene testing.

The largest impact which NGS would have (in raw numbers), is an additional 2.5% of patients being found with *EGFR* variants. This was due in part to NGS having a higher level of analytical sensitivity (a lower threshold of detection) than Sanger sequencing, the cobas assay and some other PCR tests, although NGS had a higher threshold of detection than ARMS-PCR. The population criteria for *EGFR* TKIs on the PBS do not specify a threshold for positivity, so the use of tests with a higher level of sensitivity would identify more patients eligible for TKIs, despite

⁵ 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.

these patients potentially having a different spectrum of disease than those in the key trials used to establish the clinical utility of the test-drug codependency. In addition, NGS detected some rare variants not able to be detected by all the methods of single-gene testing. For example, Tan et al. (2020)⁶ reported that NGS identified an additional 12 variants, of which 7 (58%) were common variants (ex19del, L858R or T790M), and 5 (42%) were rare variants. Similarly, Park et al. (2020) reported that of the 16 incremental *EGFR* variants identified by NGS, 8 were in hotspot locations (in regions tested by PCR, but below the sensitivity threshold), and the remaining 8 were in locations not tested by PCR, although half of the rare variants identified were considered actionable, and *EGFR* TKIs were administered. The majority (but not all) of the additional 2.5% with *EGFR* variants would therefore be considered to have “activating variants” conferring sensitivity to *EGFR* TKIs.

The largest relative difference was the number of patients identified with *ALK* rearrangements. Four studies used the same threshold for positivity as the PBS restrictions for *ALK* TKIs ($\geq 15\%$ of cells with staining on FISH), and had similar results (PPA 91%, NPA 99%) to studies which used a lower threshold ($\geq 10\%$, $k=2$) or did not specify the threshold for positivity ($k=5$) (PPA 92%, NPA 99%). Results for *ROS1* and *MET*ex14sk were highly concordant between testing methods.

Table 6 Summary of concordance data between NGS and single-gene testing

Gene	Evidence base	PPA (95%CI)	NPA (95%CI)	Prevalence	Per 1000 successfully tested (95%CI)				PPV (95%CI)	NPV (95%CI)
					NGS+ /SG+	NGS+ /SG-	NGS- /SG+	NGS- /SG-		
<i>EGFR</i>	n=2611 k=22	0.98 (0.95, 0.99)	0.97 (0.95, 0.99)	15% ^a	147 (143, 149)	25 (8, 42)	3 (1, 7)	825 (808, 842)	0.85	1.00
<i>ALK</i>	n=1464 k=11	0.92 (0.77, 0.97)	0.99 (0.93, 1.00)	3% ^b	28 (23, 29)	10 (0, 68)	2 (1, 7)	960 (902, 97)	0.74	1.00
<i>ROS1</i>	n=830 k=6	0.86 (0.63, 0.96)	1.00 (0.99, 1.00)	1.61% ^c	14 (10, 15)	0 (0, 10)	2 (1, 6)	984 (974, 984)	1.00	1.00
<i>MET</i> ex14sk	n=99 k=1	0.98 (0.89, 1.00)	1.00 (0.93, 1.00)	3.6% ^d	35 (32, 36)	0 (0, 69)	1 (0, 4)	964 (895, 964)	1.00	1.00
Total					224	35	8	733		

^aBased on p18 [MSAC 1161 PSD](#), November 2012

^bBased on p5 [MSAC 1250.1 PSD](#), November 2014

^cBased on p12 [MSAC 1454 PSD](#), July 2018

^dBased on Table 11, p27 [Tepotinib PBAC PSD](#), November 2021

ALK = ALK receptor tyrosine kinase; *EGFR* = epidermal growth factor receptor; *MET* = mesenchymal-epithelial transition; NGS = next generation sequencing; NPA = negative percent agreement; NPV= negative predictive value; PPA = positive percent agreement; PPV = positive predictive value; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase; SG = single-gene testing

The superiority of targeted therapies over non-targeted therapies for those with biomarkers has been demonstrated in submissions to the PBS for erlotinib, gefitinib, afatinib, osimertinib, crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, entrectinib, and tepotinib. Steeghs et al. (2022)¹ reported that NGS had a higher success rate, higher sensitivity, and was more comprehensive than sequential single-gene testing, and consequently, a higher yield of

⁶ Tan A, et al. (2020). Utility of incorporating next-generation sequencing (NGS) in an Asian non-small cell lung cancer (NSCLC) population: Incremental yield of actionable alterations and cost-effectiveness analysis. *Lung Cancer*, vol. **139**, January, pp. 207-215

actionable variants. This should therefore result in a higher proportion of patients receiving targeted therapies, and result in superior health outcomes.

Change in management data were scant (six small before-and-after case series) but suggested that in cases where NGS identified actionable variants missed by sequential single gene testing, targeted treatment was initiated in a median of 50% of cases (range 17.6% to 100%). (Note, insufficient information was provided to determine whether those variants considered actionable in the studies would also be considered eligible for PBS-listed targeted treatments).

Targeted searches were performed to identify evidence on whether patients with low allele frequency or rare variants responded to *EGFR* TKIs in the same manner as patients selected by the clinical utility standards. A systematic review was identified comparing *EGFR* TKI treatment effectiveness in those with common sensitising variants (ex19del or L858R⁷), the common resistance conferring variant (T790M) and rare variants (any other variants)⁸. The results were heterogeneous, and not meta-analysed due to differences in the method of grouping variants. Those with exon 20 variants were less likely to respond to the listed *EGFR* TKIs than those with common sensitising variants, and a number of exon 20 insertions were considered to have some evidence of conferring resistance to *EGFR* TKIs. Those with variants in exon 18 (such as variant G719X) frequently responded well to *EGFR* TKIs, so this variant may now be considered likely to confer sensitivity to *EGFR* TKIs. Therefore, currently, the benefit of having additional rare variants identified due to using NGS is mixed. Eligibility for *EGFR* TKIs will depend on whether the report provided by pathologists to the treating clinician, defines the actionability of the identified variants. In the future, it is expected that targeted treatment for those with exon 20 insertions will become available in Australia, which should increase the proportion of patients who benefit from having rare variants identified.

⁷ These common sensitising variants align with the inclusion criteria for studies such as the EURTAC RCT of erlotinib vs chemotherapy (2012) which was part of the evidentiary basis of the test-drug co-dependency approved by MSAC/PBAC.

⁸ John T, et al. (2021). Uncommon EGFR mutations in non-small-cell lung cancer: A systematic literature review of prevalence and clinical outcomes. *Cancer Epidemiol*, vol. **76**, Feb, p. 102080

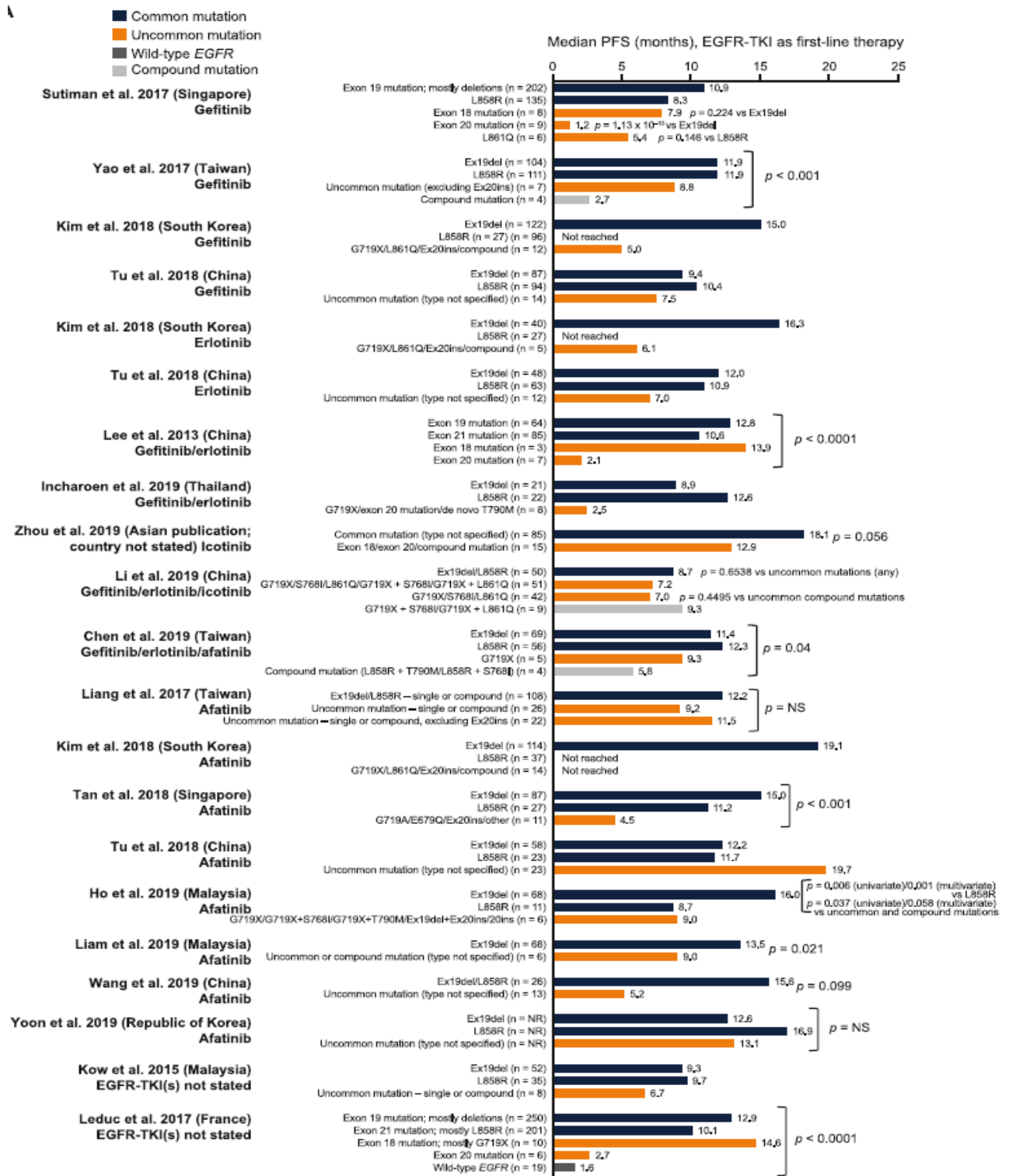


Figure 3 Progression free survival in patients with common or uncommon EGFR variants receiving EGFR-TKI as first-line therapy

NB: p-values denote comparison between common and uncommon variants.

Liang et al. "compound mutations" refers to two uncommon variants. Wu et al. (2018): L858R cohort includes four patients with both L858R and Ex19del. Ho et al. (2019): exact uncommon mutations are G719X/G719X + S768I/G719X + T790M/Ex19del + Ex20ins/Ex20ins. Lee et al. (2013) and Leduc et al. (2017): "Exon 20 mutations" do not include T790M.

Source: John et al., 2022⁹ Reproduced under Creative Commons CC-BY license.

⁹ John, T, et al. (2022), 'Uncommon EGFR mutations in non-small-cell lung cancer: A systematic literature review of prevalence and clinical

Targeted (non-systematic) searches were performed to assess whether patients with low allele frequency in tumour tissue (likely only detected by high sensitivity testing methods), responded to EGFR TKIs in the same manner as those with high allele frequency. Note that for EGFR TKIs, no threshold is defined for positivity in PBS restrictions. Three observational studies were identified, which suggested that those with a high allele frequency (i.e., a high proportion of tumour cells which have the variant identified) responded better to EGFR TKIs than those with low allele frequency. Low levels of T790M variants identified concurrently with activating EGFR variants did not significantly impact on treatment effectiveness of EGFR TKIs. Some of the additional variants detected by small NGS panels may therefore not respond to targeted therapy in the same manner as those detected by sequential single-gene testing.

Table 7 Association between variant allele frequency and response to treatment

Study	Population	Intervention	Outcome	Results
Friedlaender et al. (2021) ¹⁰ Switzerland	42 patients with NSCLC and EGFR variants Threshold for high vs low allelic frequency: 0.30	NGS using IonAmpliseq Hotspot Panel V2 Treatment with EGFR TKI	PFS	High vs low: HR = 0.27 (95%CI 0.09, 0.79, p=0.017)
			OS	High vs low: HR = 0.47 (95%CI 0.17, 1.30, p=0.14)
Gieszer et al. (2021) ¹¹ Hungary	89 Caucasian patients with NSCLC (adenocarcinomas), and EGFR variants Adjusted VAF (aVAF) = VAF/TC% x 100	Therascreen EGFR Pyro assay Erlotinib or gefitinib as first- or second-line treatment	PFS	Positive linear correlation between aVAF and PFS: r = 0.319, p=0.003, Spearman's correlation
			PFS	Adjusting for clinicopathological variables (age, gender, variant, treatment, treatment line): HR = 0.991 (95%CI 0.982, 0.999, p=0.042)
			OS	High vs low aVAF median 94 vs 57 weeks, p=0.011
Ye et al. (2021) ¹² Australia	64 patients with NSCLC and EGFR variants, with stage IV disease 14 VAF <0.1% 28 VAF ≥0.1% 1 detectable by SS, VAF = 28.5%	Digital PCR Erlotinib or gefitinib	PFS	No significant difference by T790M status (log rank test p = 0.897), or T790M allele frequency (<0.1 vs ≥0.1%, p=0.515)

HR = hazard ratio; NSCLC = non-small cell lung cancer; OS = overall survival; PCR = polymerase chain reaction; PFS = progression free survival; SS = Sanger sequencing; TC = estimated percentage of neoplastic cells; VAF = variant allele frequency, percentage of alleles determined by the assay to have EGFR variants

One of the claims made by the applicant was that NGS returns results faster than sequential single-gene testing. Three cohort studies were identified which compared turnaround times and reported that NGS was 0 to 3 days faster than sequential single-gene testing strategies. The 3-day saving in turnaround time was reported when a combined DNA and RNA panel was used¹³. In

outcomes', *Cancer Epidemiol*, vol. **76**, Feb, p. 102080.

¹⁰ Friedlaender, A, et al. (2021), 'The Impact of Variant Allele Frequency in EGFR Mutated NSCLC Patients on Targeted Therapy', *Front Oncol*, vol. **11**, p. 644472.

¹¹ Gieszer, B, et al. (2021), 'EGFR variant allele frequency predicts EGFR-TKI efficacy in lung adenocarcinoma: a multicenter study', *Transl Lung Cancer Res*, vol. **10**, no. 2, Feb, pp. 662-674.

¹² Ye, L, et al. (2020), 'Detection of Low-level EGFR c.2369 C > T (p.Thr790Met) Resistance Mutation in Pre-treatment Non-small Cell Lung Carcinomas Harboring Activating EGFR Mutations and Correlation with Clinical Outcomes', *Pathol Oncol Res*, vol. **26**, no. 4, Oct, pp. 2371-2379.

¹³ Dall'Olio, FG, et al. (2020), 'Comparison of Sequential Testing and Next Generation Sequencing in advanced Lung Adenocarcinoma patients - A single centre experience', *Lung Cancer*, vol. **149**, November, pp. 5-9.

a large study from the Netherlands, no difference to sequential single gene testing was reported, when a DNA panel was used in combination with either IHC, FISH or an RNA panel (Steeghs et al. (2022)). These data are likely to be more applicable to the Australian setting in the near future, as not many laboratories are currently able to use NGS on both DNA and RNA simultaneously. However, as more laboratories develop the ability to perform simultaneous NGS testing, and as more biomarkers are deemed relevant by MSAC/PBAC, the difference in turnaround time between NGS and sequential single gene testing is expected to increase.

Table 8 Turnaround time for NGS vs sequential single-gene testing strategy

Study	Population	Intervention (NGS)	Comparator (SG)	Turnaround time for NGS	Turnaround time for comparator	Difference
Dall'Olio et al. (2020) ¹³	N=537 Consecutive NSCLC (adenocarcinoma) patients	Oncomine Focus Assay on DNA and RNA	Single gene (<i>EGFR</i> , <i>KRAS</i> , <i>BRAF</i> , <i>MET</i> or <i>HER2</i>), IHC and FISH	Mean 10 working days	Mean 13.15 days	-3.15 days
Li et al. (2021) ³	884 newly diagnosed, treatment-naïve metastatic NSCLC patients with limited tissue sample	NGS on DNA only	ARMS-PCR and IHC/FISH	Median 12 business days (range 5 - 79 days)	Median 13 business days (range 9 – 86)	-1 day
Steeghs et al. (2022) ¹	Stage IV NSCLC patients. 3343 NGS patients, 698 non-NGS patients	NGS on DNA, plus fusions tested by IHC, FISH or RNA NGS	Various non-NGS single gene testing such as ICH and FISH used throughout clinical practice in the Netherlands	Median 10 days (range 0 - 495; IQR 7 – 14)	Median 10 days (range 2 – 63; IQR 7 – 13)	0 days

ARMS-PCR = amplification-refractory mutation system polymerase chain reaction; DNA = deoxyribonucleic acid; *EGFR* = epidermal growth factor receptor; FISH = fluorescent *in situ* hybridisation; IHC = immunohistochemistry; *KRAS* = KRAS proto-oncogene, GTPase; NGS = next generation sequencing; NSCLC = non-small cell lung cancer; RNA = ribonucleic acid; SG = single-gene testing

The clinical implications of faster initiation of targeted treatment are unclear. No studies could be found which focused on the health implications of the timeliness of targeted treatments (i.e. prompt vs delayed targeted treatment). However, a systematic review was identified which compared health outcomes in those with advanced NSCLC who received timely vs untimely first-line untargeted treatment (surgery, radiotherapy, chemotherapy, or any treatment), and reported that those treated faster had worse outcomes¹⁴. This “waiting time paradox” is likely due to patients with more symptoms (and worse prognosis) being treated faster, and those treated palliatively receiving more timely care than those treated with curative intent.

Clinical claim

The evidence supported the clinical claim of superior effectiveness due to more patients being identified with variants by small NGS panels than sequential single gene testing (moderate level of confidence). The majority of these additional patients would be considered eligible for PBS-listed targeted treatments with the proposed changes to restrictions. The additional patients with

¹⁴ Hall, H, et al. (2022) 'Association between time-to-treatment and outcomes in non-small cell lung cancer: a systematic review', *Thorax*, Aug;77(8):762-768..

actionable variants identified are then able to be managed with targeted treatment, which may result in superior health outcomes (low confidence).

The evidence also supported the clinical claim of superior safety, due to the likelihood that the more efficient use of tumour tissue by NGS than sequential single gene testing (moderate confidence) would result in fewer rebiopsies being performed (low confidence) and avoiding biopsies would reduce the risk of adverse events associated with biopsies (moderate confidence).

13. Economic evaluation

The clinical claim of superiority was made based on:

- an improvement in the test success rate (i.e., more samples with sufficient quantity and/or quality to be able to be successfully tested for variants); and
- an improvement in the yield of variants identified due to being more comprehensive (identifying “in scope” and “beyond restriction” variants) and more sensitive (detecting in-scope variants at a lower variant allelic frequency).

Therefore, a cost-effectiveness analysis was presented based on the results of the linked evidence approach. No evidence was identified to enable modelling changes in treatment, and given the following uncertainties, the model presented was truncated at the point of treatment:

- Variants that can be identified by either current or proposed testing (referred to in the analysis as “common” variants) result in the use of targeted therapies. In patients with common variants that are missed by proposed small gene panel testing (due to discordant results or unsuccessful testing and unsuccessful rebiopsy) or those that are missed by current testing (due to IHC triage or unsuccessful testing and unsuccessful rebiopsy), patients may receive standard of care (SoC) in place of targeted therapies. Quantifying the foregone benefit associated with the treatment of common variants with SoC is difficult because, in many cases, SoC has evolved since the initial trials of targeted therapies. No evidence was identified in the clinical evaluation to quantify the benefit of targeted therapies compared with SoC in patients with common variants.
- Variants that can only be identified through small gene panel testing are referred to in the analysis as “incremental” variants, and include variants both within the current scope of eligibility to PBS-listed targeted therapies (due to detection of lower allelic frequencies and some additional *EGFR* variants known to confer sensitivity to TKIs), and those beyond current PBS restrictions. Notably, given the absence of current MBS reimbursement for NTRK testing in patients with NSCLC, all NTRK variants detected by panel testing are by definition incremental variants. Best estimates from the clinical evidence base suggest that the majority of these patients would be eligible for PBS-listed targeted treatments; however, these patients may have a different spectrum of disease than those in the key trials of the targeted therapies. Therefore, treatment response and duration of treatment in patients with these incremental variants to both targeted therapy and SoC is uncertain, and so the benefits and costs that may be associated with changing treatment from SoC to targeted therapy associated with these incremental variants are also uncertain.
- In addition to the issues regarding quantifying the differences in outcomes with proposed small gene panel testing, the modelled costs of any analyses that attempt to capture outcomes due to changes in treatment would likely be affected by existing special price

arrangements for targeted therapies and immunotherapies. Analyses based on the published prices would not reflect the accepted cost-effectiveness of the included therapies, and the cost-effectiveness of proposed small gene panel testing would be influenced by confidential discounts applied to both targeted therapies and immunotherapies.

The analysis presented was therefore a cost-effectiveness analysis where the primary outcome reported was the net change in patients determined to be eligible for targeted therapy. This outcome was disaggregated by type of actionable variant identified (i.e. common or incremental).

A stepped approach was used to generate the base case analysis that incorporated different aspects of the linked evidence separately to distinguish the effect of each of these on the results. Further, incremental yield data with proposed panel testing have been adjusted in the economic analysis to reflect some IHC ± FISH expected in practice and to reflect comparisons to the clinical utility standard. Test success data have also been transformed to reflect implications of rebiopsies due to insufficient quantity or quality of tissue. These translations of the clinical evidence for use in the model have been added in separate steps. Other key model assumptions – RNA panel use restricted to an absence of *KRAS* and *BRAF* variants, and use of testing in patients who do not progress to advanced disease – have also been incorporated in separate steps.

A summary of the key components of the economic evaluation is presented in Table 9.

Table 9 Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Patients with non-squamous or NOS NSCLC
Prior testing	Histopathology testing to confirm tumour histology
Comparator	Single gene testing (reflex <i>EGFR</i> , ALK IHC and ROS1 IHC, followed by, if relevant, reflex ALK FISH and/or ROS1 FISH, and METex14sk testing)
Type(s) of analysis	Cost-effectiveness analysis
Outcomes	Primary: Patients eligible for targeted therapy, disaggregated by patients with common and incremental variants identified Additional: Patients with actionable (i.e. common and incremental variants) variants identified, patients with known biomarker status; changes in rebiopsies required
Time horizon	Time to first-line treatment decisions in the advanced NSCLC setting
Computational method	Decision analytic
Generation of the base case	Modelled stepped analysis, incorporating different aspects of the linked evidence, translations of the clinical evidence and other key model assumptions separately to distinguish the effect of each of these on the results.
Transition probabilities	Yield of actionable variants: Accepted estimates of variant yield as identified by the clinical utility standard ('common' variants), adjusted for additional variants identified by small gene panel testing in the same biomarker ('incremental' variants) using concordance estimates derived in the clinical evaluation. Yield estimates were adjusted to reflect some IHC ± FISH use following small DNA panel testing (in instances where tissue quantity or quality is insufficient for RNA panel testing). Success of testing was also based on estimates presented in the clinical evaluation.
Discount rate	Not applicable
Software	TreeAge Pro and Microsoft Excel

ALK = ALK receptor tyrosine kinase; DNA = deoxyribose nucleic acid; *EGFR* = epidermal growth factor receptor; FISH = fluorescence *in situ* hybridisation; IHC = immunohistochemistry; METex14sk = MET proto-oncogene, receptor tyrosine kinase exon 14 skipping alterations; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; RNA = ribonucleic acid; ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase.

The results of the stepped analysis to generate the base case economic evaluation is presented in Table 10. The steps that had the most effect on the results of the analysis included restricting RNA-only panel testing to those without *KRAS* and *BRAF* activating variants; applying an increase in variant yield with panel testing, the inclusion of patients tested with early-stage disease who do not progress; and including costs and outcomes related to rebiopsy.

Table 10 Results of the stepped economic analysis

	Small gene panel testing	Single gene testing	Increment
Step 1: Test cost difference only			
No difference in success or yield between current and proposed testing. In two-stage panel testing, patients with <i>KRAS</i> or <i>BRAF</i> variants receive RNA testing.			
Total cost	\$1,240.55	\$894.72	\$345.83
Step 2: RNA panel testing restricted to <i>EGFR</i>, <i>KRAS</i>, <i>BRAF</i> and <i>MET</i> negatives			
As per the proposed small RNA gene panel test item, where two-stage panel testing is used, patients found with <i>KRAS</i> or <i>BRAF</i> variants <u>cannot</u> receive RNA testing.			
Total cost	\$1,093.43	\$894.72	\$198.72
Step 3: Incorporate differences in test success across model arms			
Sufficient sample is available for testing in 97.2% of patients tested with small gene panels, compared to 94.6% with single gene testing, based on Steeghs et al. (2022) ^a (Section 10). As proposed testing can only be claimed once per episode of disease and cannot be claimed in addition to single gene items, where testing is not successful due to insufficient sample, no cost of testing is assumed to apply in either model arm.			
Total cost	\$1,062.82	\$846.40	\$216.42
Proportion with an actionable variant identified ^b	0.2256	0.2196	0.0060
ICER per additional patient with an actionable variant identified			\$35,862
Step 4: Incorporate differences in yield across model arms			
Concordance data of small gene panel testing, relative to the respective single gene test, is incorporated (Table 6, Section 10). Where PPA < 1, some variants that may have otherwise been identified through single gene testing may be missed, and where NPA < 1 additional "in scope" and "beyond restriction" variants are identified. As the majority of small gene panel testing uses the two-step method, with more variants identified on the small DNA panel, fewer small RNA panels may be required (and so a reduction in small gene panel test cost is observed).			
Total cost	\$1,052.71	\$846.40	\$206.30
Proportion with an actionable variant identified ^b	0.2517	0.2196	0.0321
ICER per additional patient with an actionable variant identified			\$6,425
Step 5: Adjust <i>ALK</i> concordance for comparison to clinical utility standard			
The concordance of small gene panel testing to single gene test methods for <i>ALK</i> in Table 6 was based on a comparison of NGS to FISH ± IHC, whereas the clinical utility standard used in the trials for <i>ALK</i> targeted therapy was FISH (≥15% positive cells). Only one study that compared small gene panel testing to FISH reported using this same definition of positivity (Park and Shim 2020) ^c . PPA of <i>ALK</i> and <i>ROS1</i> IHC relative to FISH was also incorporated.			
Total cost	\$1,052.71	\$846.40	\$206.30
Proportion with an actionable variant identified ^b	0.2526	0.2184	0.0342
ICER per additional patient with an actionable variant identified			\$6,026

	Small gene panel testing	Single gene testing	Increment
Step 6: Adjust for some IHC ± FISH use with proposed testing			
The applicant expected that 5–10% of tests would require current testing methods. MSAC have previously considered that small DNA panels are currently being used for <i>EGFR</i> testing (MSAC 1669 PSD, March 2022 MSAC Meeting) and so this has been assumed to apply to small RNA gene panels only, as RNA panels may have larger sampling requirements. This reduces both the cost of proposed testing and also yield (as additional “in scope” and “beyond restriction” variants would not be identified in this proportion of patients)			
Total cost	\$1,035.55	\$846.40	\$189.15
Proportion with an actionable variant identified ^b	0.2523	0.2184	0.0339
ICER per additional patient with an actionable variant identified			\$5,582
Step 7: Incorporate patients with early disease who do not progress			
Small gene panel testing is proposed to occur on diagnosis of non-squamous or NOS NSCLC. While current <i>EGFR</i> and <i>ALK</i> and <i>ROS1</i> IHC testing also occur at diagnosis, <i>ALK</i> and <i>ROS1</i> FISH and proposed <i>MET</i> ex14sk testing do not occur until the development of advanced disease. The analysis therefore has been adjusted to reflect that not all patients who receive small gene panel testing would develop advanced disease (and so would not be eligible for targeted therapy, currently available only in the advanced setting).			
Total cost	\$1,035.54	\$743.77	\$291.76
Proportion eligible for targeted therapy	0.1913	0.1656	0.0257
ICER per additional patient eligible for targeted therapy			\$11,352
Step 8: Incorporate rebiopsies			
In those with insufficient sample for testing, rebiopsy is attempted where 20% are assumed to fail (Kelly et al. 2019) ^d .			
Total cost	\$1,173.23	\$1,004.20	\$169.02
Proportion eligible for targeted therapy	0.1957	0.1732	0.0225
ICER per additional patient eligible for targeted therapy			\$7,496

^a Steeghs, EMP, et al (2022), 'Mutation-tailored treatment selection in non-small cell lung cancer patients in daily clinical practice', *Lung Cancer*, vol. 167, May, pp. 87-97.

^b Incorporates variants that could be identified by either current or proposed testing, or incremental variants within the current scope of eligibility to PBS-listed targeted therapies, and those beyond current PBS restrictions.

^c Park, E et al. (2020), 'Detection of targetable genetic alterations in Korean lung cancer patients: A comparison study of single-gene assays and targeted next-generation sequencing', *Cancer Res Treat*, vol. 52(2), pp. 1-9.

^d Kelly, RJ, et al. (2019), 'Complications and Economic Burden Associated With Obtaining Tissue for Diagnosis and Molecular Analysis in Patients With Non-Small-Cell Lung Cancer in the United States', *J Oncol Pract*, vol. 15, no. 8, Aug, pp. e717-e727.

ALK = ALK receptor tyrosine kinase; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; DNA = deoxyribonucleic acid; *EGFR* = epidermal growth factor receptor; FISH = fluorescence *in situ* hybridisation; IHC = immunohistochemistry; *KRAS* = KRAS proto-oncogene, GTPase; *MET*ex14sk = MET proto-oncogene, receptor tyrosine kinase exon 14 skipping alterations; NGS = next-generation sequencing; NOS = not otherwise specified; NPA = negative percent agreement; NSCLC = non-small cell lung cancer; PPA = positive percent agreement; RNA = ribonucleic acid; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase.

Disaggregated costs and outcomes are presented in Table 11.

Table 11 Disaggregated modelled costs and outcomes

	Small gene panel testing	Single gene testing	Increment
Disaggregated costs			
Cost of testing	\$1,053.65	\$773.59	\$280.06
Cost of rebiopsy	\$119.58	\$230.61	-\$111.03
Total cost	\$1,173.23	\$1,004.20	\$169.02
Disaggregated outcomes			
Eligible for targeted therapy	0.1957	0.1732	0.0225
• Common variants	0.1706	0.1732	-0.0026
• Incremental variants	0.0251	0.0000	0.0251
Actionable variant identified	0.2556	0.2075	0.0481
• Common variants identified	0.2226	0.2075	0.0152
• Incremental variants identified	0.0330	0.0000	0.0330
Patients successfully tested	0.9890	0.9788	0.0102
Proportion with known biomarker status	0.9817	0.7583	0.2234
Proportion undergoing rebiopsy	0.0212	0.0410	-0.0197

The additional patients eligible for targeted therapy was driven by an increase in patients with incremental variants identified. A slight reduction in patients with common variants was also observed (due to PPA < 1 applied for small gene panel testing, offset to some extent by improvement in patients successfully tested). As the incremental variants were not identified using the same testing method as was used in the clinical trials of targeted therapy, it is unclear whether all of these patients would respond to targeted therapies to the same extent as those with common variants.

More patients were identified with actionable variants (i.e. combined common and incremental variants) than those considered eligible for targeted therapy (absolutely and incrementally). This was due to the inclusion of patients tested with early stage disease who do not develop advanced disease (and so are not eligible for targeted therapy). The incremental difference was also higher (and in some cases the direction of the effect changed) due to incomplete current testing performed (i.e. not FISH or *MET*ex14sk testing).

The key drivers of the model are presented in Table 12.

Table 12 Key drivers of the model

Description	Method/Value	Impact Base case: \$7,496 per additional patient eligible for TT
Proportion patients with advanced disease (inc. those who progress)	Distribution of stage at diagnosis was based on a retrospective analysis of Victorian Cancer Registry data (Mitchell et al. 2013) ^a ; 65.5% were advanced at diagnosis. Of those diagnosed with Stages I-IIIa disease, 30% are assumed to experience progression. Therefore, 75.9% of patients diagnosed with non-squamous NSCLC are modelled to have (or reach) an advanced disease stage.	The proportion is uncertain. The ICER is highly sensitive to changes in this estimate. Increasing the proportion to 100% reduces the ICER to \$941 per additional patient eligible for TT, whereas decreasing this to 50%, increases the ICER to \$21,530.
Small gene panel concordance	Based on the systematic literature review of concordance conducted during the clinical evaluation. Given differences between the comparator used for <i>ALK</i> concordance (FISH ± IHC, with varied definitions of FISH positivity) in the meta-analysis, the data most aligned with the clinical utility standard was used in the base economic analysis.	The analyses were highly sensitive to the NPA values used (as these determine the incremental variants identified through small gene panel testing). The ICER was most sensitive to <i>EGFR</i> NPA values, where the range in ICERs observed was \$4,562–\$18,168 per additional patient eligible for TT.
RNA panel use	Where separate DNA then RNA panels are used, only those without <i>EGFR</i> , <i>MET</i> , <i>KRAS</i> and <i>BRAF</i> variants are assumed to receive further RNA panel testing (as per the proposed item descriptor).	The analysis is highly sensitive to this assumption. Where testing is allowed in those with <i>KRAS</i> and <i>BRAF</i> variants, the ICER per additional patient eligible for TT increases to \$13,627.
Test success	Based on Steeghs et al. (2022) ^b : <ul style="list-style-type: none"> • Small gene panel testing: 97.2% • Single gene testing: 94.6% 	The ICER is moderately sensitive to the difference between strategies. Where there is no difference, the ICER increases to \$12,829 per additional patient eligible for TT, however when the difference doubles (from 2.6% to 5.2%), the ICER decreases to \$2,731.
Rebiopsy	100% where testing was not successful. Rebiopsy was associated with a 20% failure rate (Kelly et al. 2019) ^c and a 14% complication rate (1161 PSD, November 2012 MSAC Meeting). The base case assumed all rebiopsies occurred in the outpatient setting, with cost based on AR-DRG E42A, B and C.	The analysis was moderately sensitive to the uptake of rebiopsy and to a lesser extent, cost. Reducing the rebiopsy rate to 60% increased the ICER per additional patient eligible for TT to \$9,161. Assuming all rebiopsies occur in an outpatient setting increased the ICER to \$9,475

^a 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.

^b Steeghs, EMP, et al. (2022), 'Mutation-tailored treatment selection in non-small cell lung cancer patients in daily clinical practice', *Lung Cancer*, vol. 167, May, pp. 87-97.

^c Kelly, RJ, et al. (2019), 'Complications and Economic Burden Associated With Obtaining Tissue for Diagnosis and Molecular Analysis in Patients With Non-Small-Cell Lung Cancer in the United States', *J Oncol Pract*, vol. **15**, no. 8, Aug, pp. e717-e727.

ALK = ALK receptor tyrosine kinase; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; DNA = deoxyribose nucleic acid; *EGFR* = epidermal growth factor receptor; FISH = fluorescence *in situ* hybridisation; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; *KRAS* = KRAS proto-oncogene, GTPase; *MET* = MET proto-oncogene, receptor tyrosine kinase; NPA = negative percent agreement; NSCLC = non-small cell lung cancer; RNA = ribonucleic acid; TT = targeted therapy.

The results of key sensitivity analyses are presented in Table 13.

Table 13 Results of the key sensitivity analyses

	Inc. cost	Inc. eligible for targeted therapy	ICER	% change
Base case	\$169.02	0.0225	\$7,496	-
Proportion of patients with advanced disease (base case: 75.9%)				
100%	\$27.97	0.0297	\$941	-87%
50%	\$320.01	0.0149	\$21,530	187%
Timing of <i>METex14sk</i> testing (base case: after <i>EGFR</i>)				
At the same time as <i>EGFR</i>	\$109.54	0.0225	\$4,858	-35%
After <i>EGFR</i> (excluding block retrieval and consult costs)	\$252.67	0.0225	\$11,206	49%
Small gene panel testing strategy (base case: mixed)				
All combined DNA/RNA panel testing	\$348.65	0.0228	\$15,277	104%
All two-stage DNA then RNA panel testing	\$116.98	0.0228	\$5,126	-32%
All DNA then IHC/FISH testing	-\$162.34	0.0173	Dominant	-225%
Test success (base case: 97.2% for panels, 94.6% for single-gene testing)				
Both strategies 97.2%	\$273.97	0.0216	\$12,662	69%
97.2% for panels, 95.9% ^a for single-gene testing	\$221.50	0.0221	\$10,026	34%
97.2% for panels, 92.0% ^b for single-gene testing	\$64.07	0.0235	\$2,731	-64%
<i>ALK</i> small gene panel concordance (base case: vs clinical utility standard, FISH ≥15% positivity)				
<i>ALK</i> small gene panel concordance vs FISH ± IHC #1	\$168.99	0.0219	\$7,730	3%
<i>ALK</i> small gene panel concordance vs FISH	\$169.00	0.0360	\$4,697	-37%
Small panel concordance				
<i>ALK</i> NPA, 0.97 (base case: 0.99)	\$169.02	0.0375	\$4,509	-40%
<i>ALK</i> NPA, 1.00 (base case: 0.99)	\$169.02	0.0166	\$10,162	36%
<i>ALK</i> PPA, 0.48 (base case: 1.00)	\$168.81	0.0114	\$14,848	98%
<i>EGFR</i> NPA, 0.95 (base case: 0.97)	\$161.36	0.0354	\$4,562	-39%
<i>EGFR</i> NPA, 0.99 (base case: 0.97)	\$176.69	0.0097	\$18,168	142%
<i>METex14sk</i> NPA, 0.93 (base case: 1.00)	\$138.59	0.0734	\$1,887	-75%
Rebiopsy uptake rate (base case: 100%)				
30%	\$254.94	0.0248	\$10,298	37%
60%	\$218.12	0.0238	\$9,161	22%
Average fee charged for <i>EGFR</i> and <i>ALK</i> and <i>ROS1</i> FISH (base case: MBS Schedule Fees)	\$185.26	0.0225	\$8,217	10%
FISH utilisation, use IHC NPA data (base case: calibrated) ^c #2	\$183.78	0.0225	\$8,151	9%
Separate RNA small panel use, allowed with <i>KRAS</i> or <i>BRAF</i> #4 (base case: not allowed)	\$307.24	0.0225	\$13,627	82%
Proportion with <i>KRAS</i> or <i>BRAF</i> activating variants, 52% (base case: 30.8%)	\$73.89	0.0225	\$3,277	-56%
Rebiopsy cost, \$3,369 [all outpatient] #3 (base case: \$5,630 [all inpatient])	\$213.63	0.0225	\$9,475	26%

	Inc. cost	Inc. eligible for targeted therapy	ICER	% change
Base case	\$169.02	0.0225	\$7,496	-
Multivariate analyses				
#1 AND #2	\$183.74	0.0219	\$8,404	12%
#1, #2 AND #3	\$228.35	0.0219	\$10,444	39%
#1, #2, #3 AND #4	\$366.57	0.0219	\$16,767	124%

^a Half the difference between test strategies

^b Double the difference between test strategies

^c Estimates of FISH use in the base case was calibrated to MBS utilisation data on the ratio of *EGFR:ALK* or *ROS1* FISH services. The sensitivity analysis uses estimates based on biomarker prevalence and IHC specificity.

ALK = ALK receptor tyrosine kinase; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; DNA = deoxyribose nucleic acid; *EGFR* = epidermal growth factor receptor; FISH = fluorescence *in situ* hybridisation; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; *KRAS* = KRAS proto-oncogene, GTPase; *METex14sk* = MET proto-oncogene, receptor tyrosine kinase exon 14 skipping alterations; NPA = negative percent agreement; *NTRK* = neurotrophic receptor tyrosine kinase 1; PPA = positive percent agreement; RNA = ribonucleic acid; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase.

The analyses were most sensitive to the proportion of patients with advanced disease (as this affects the current costs offset), the small gene panel testing strategy used (including distribution of strategies used), differences in the test success rate, concordance of small gene panel testing (particularly NPA, which is assumed to increase incremental variants with small gene panel testing), and rebiopsy rate. The analysis was also sensitive to the assumption that patients found to have *KRAS* and *BRAF* variants on the DNA panel only would not receive RNA small gene panel testing (and expected yield of these non-actionable variants). Instances of concurrent variants may be more common than previously thought. A prospective case series¹⁵ from Germany reported that of all patients with *ROS1* and *ALK* variants identified, respectively, 23.7% (14/59) and 16.1% (19/118) also had variants in *BRAF* or *KRAS*.

A few assumptions included in the base case analysis may not be the most conservative approach. Justification has been provided to support the use of the estimates in the base case, however multivariate analyses are performed using alternate approaches identified. The results do suggest that the analyses are sensitive to the combined effects of these changes.

14. Financial/budgetary impacts

A market-share approach was used to estimate the extent of use of small gene panel testing in patients with non-squamous NSCLC with MBS listing. This was based on projections of current *EGFR* service use and current use of *ALK* and *ROS1* FISH services relative to *EGFR* services. *METex14sk* testing has also recently been recommended by MSAC in this patient population. Epidemiological estimates are applied to the projections of *EGFR* use to estimate the change in use and cost related to *METex14sk* testing.

The financial implications to the MBS resulting from the proposed listing of small gene panel testing are summarised in Table 14. Note that these projections are currently by calendar year.

¹⁵ Griesinger, F, et al. (2021), 'Biomarker testing in non-small cell lung cancer in routine care: Analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315)', *Lung Cancer*, vol. **152**, Feb, pp. 174-184.

Table 14 Net financial implications of small gene panel testing to the MBS

Parameter	2023	2024	2025	2026	2027	2028
Estimated use and cost of the proposed health technology						
Size of the <i>EGFR</i> testing market	5,521	5,797	6,074	6,351	6,628	6,905
Share of the <i>EGFR</i> testing market (100%)	5,521	5,797	6,074	6,351	6,628	6,905
Number of services of small gene panel testing	7,425	7,798	8,030	8,250	8,458	8,493
• Combined DNA/RNA (MBS benefit: \$1,087.92) ^a	1,380	1,449	1,822	2,223	2,651	3,453
• DNA only (MBS benefit: \$568.17) ^b	4,140	4,348	4,252	4,128	3,977	3,453
• RNA only (MBS benefit: \$568.17) ^b	1,905	2,000	1,956	1,899	1,829	1,588
Cost to the MBS	\$4,936,022	\$5,183,631	\$5,509,717	\$5,842,958	\$6,183,354	\$6,620,116
Change in use and cost of other health technologies						
Reduction in use of comparator testing services						
• <i>EGFR</i> (MBS benefit: \$325.13) ^c	5,521	5,797	6,074	6,351	6,628	6,905
• <i>ALK</i> FISH (MBS benefit: \$325.80) ^d	245	257	270	282	295	308
• <i>ROS1</i> FISH (MBS benefit: \$325.80) ^d	408	428	449	470	491	513
• <i>METex14sk</i> (MBS benefit: \$337.75) ^e	3,559	3,738	3,916	4,095	4,273	4,452
Reduction in use of block retrieval services (MBS benefit: \$72.25) ^f	3,559	3,738	3,916	4,095	4,273	4,452
Net change in costs to the MBS	\$3,466,662	\$3,640,562	\$3,814,751	\$3,988,966	\$4,163,208	\$4,337,803
Net financial impact to the MBS	\$1,469,360	\$1,543,069	\$1,694,966	\$1,853,992	\$2,020,147	\$2,282,313

Source: 'Section 4.4' worksheet of the '1721 financial impact.xlsx' workbook accompanying the DCAR.

ALK = ALK receptor tyrosine kinase; DNA = deoxyribose nucleic acid; *EGFR* = epidermal growth factor receptor; FISH = fluorescence *in situ* hybridisation; *METex14sk* = MET proto-oncogene, receptor tyrosine kinase exon 14 skipping alterations; RNA = ribonucleic acid; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase.

^a 31.8% × \$935.25 [75% MBS benefit] + 68.2% × \$1,159.10 [85% MBS benefit]. Split of use based on MBS data for use of *EGFR* services.

^b 31.8% × \$511.80 [75% MBS benefit] + 68.2% × \$594.45 [85% MBS benefit]. Split of use based on MBS data for use of *EGFR* services.

^c 31.8% × \$298.05 [75% MBS benefit] + 68.2% × \$337.75 [85% MBS benefit]. Split of use based on MBS data for use of *EGFR* services.

^d 35.5% × \$300.00 [75% MBS benefit] + 64.5% × \$340.00 [85% MBS benefit]. Split of use based on MBS data for use of *ALK* or *ROS1* FISH services.

^e 100% × \$337.75 [85% MBS benefit]. As proposed *METex14sk* testing has not been proposed to be a pathologist determinable test, all services have been assumed to be requested in the outpatient setting.^f 100% × \$72.25 [85% MBS benefit]. Assumed for each *METex14sk* test which has been assumed to be requested in the outpatient setting.

The net financial impact estimates were most sensitive to the distribution of use of combined or sequential small gene panels and whether separate RNA panel is allowed in those found to have *KRAS* or *BRAF* activating variants. If there is substantial growth in the market due to the listing of small gene panels (e.g. if some testing currently is funded by the states, and this shifts to the MBS), then the net impact to the MBS may be higher. However, the extent of this shift is unknown.

While there may also be a change in the relative use of IHC testing items, PASC considered that the expected reduction in the cost of IHC testing for *ALK* and *ROS1* would not be straightforward to estimate (p10, 1634 Ratified PICO). The total number of IHC services is not likely to change with proposed small gene panel testing (as this is performed on diagnosis of NSCLC), and for

many patients, the item claimed will not change (where the number of antibodies tested does not change the item being charged e.g. from use of ten to eight antibodies tested). A conservative approach has been adopted in the DCAR that assumes no reduction in cost of *ALK* and *ROS1* IHC testing. The budget impact was not sensitive to an assumption that all *EGFR* services would be associated with a change in IHC item use (from 72849 [85% benefit: \$88.70] to 72847 [85% benefit: \$76.00], reduction in cost to the MBS of \$12.70).

15. Other relevant information

REDACTED

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- NGS panel testing has superior clinical effectiveness compared with sequential single gene testing.
- Safety is likely to be superior for NGS panel testing, as less tissue is required for panel testing than for single sequential gene tests. Panel testing reduces the risk of running out of tissue when sequential tests are used, resulting in need for repeat solid tissue biopsy.
- The proposed gene panel testing includes testing for *NTRK1*, *NTRK2* and *NTRK3*, which are currently not MBS-reimbursed for patients with NSCLC. However, there are currently no PBS-listed therapies for patients with NSCLC with *NTRK* variants.
- The use of liquid biopsy has not been assessed in this application.
- It may be appropriate to extend eligibility for panel testing to patients with squamous cell carcinoma (SqCC) given that compared to NSCLC, it is comparatively rare for patients with SqCC to have *EGFR* mutations (noting also that SqCC has a number of potentially targetable driver mutations in addition to *EGFR* that have not been assessed in this application).

Economic issues:

- There is some evidence that NGS is a cost-effective alternative to MBS-reimbursed single gene testing.
- In the absence of current reimbursement for *NTRK* testing in patients with NSCLC, all *NTRK* variants detected by panel testing would be classified as incremental variants and the benefits associated with identifying incremental variants are currently uncertain.
- The main driver of the ICER is from the relative outcomes of targeted therapies versus standard of care in those with uncommon actionable variants identified through small gene panel testing only. This may overestimate the benefit of the panel testing if these uncommon variants do not lead to patients being eligible for targeted therapy. ESC considered that this “overestimation” may be appropriate, as new therapies are being continually developed and this might help futureproof the application.
- It is unclear whether there may be additional quality-of-life benefits due to the shorter turnaround times associated with the panel leading to earlier initiation of test-directed treatment that are not currently captured.

Financial issues:

- Current financial estimates may be conservative insofar as there may be additional cost savings to the budget from lower-than-expected MBS utilisation, the reduction of *METS* testing and use of core needle biopsies for rebiopsy which have not been taken into account.

ESC discussion

ESC noted that this was a new application for the Medicare Benefits Schedule (MBS) listing of a small gene panel test for non-squamous non-small cell lung carcinoma (NSCLC). ESC noted that this was an expedited application that bypassed PASC.

ESC noted that MSAC had previously considered individual single gene tests for biomarker assessment in patients with NSCLC. In November 2017 (application 1454):

MSAC noted that the sequential testing of EGFR, ALK and ROS1 yield mutually exclusive treatment pathways and that sequential testing wastes tissue sample, time and is more expensive than a single panel of tests. MSAC recommended that the Department conduct a cost-utility review of gene panel and/or next generation sequencing (NGS) test options to inform these first-line therapy options ... MSAC advised that any MBS funding should be based on a gene panel or NGS test of equivalent or better analytical performance to sequential IHC and FISH testing and assurance that the average gene panel or NGS test is no more costly than the average cost of the sequential testing that it would replace. MSAC noted that overall testing may still require more than one gene panel test due to differences in lung cancer gene aberrations as somatic mutations are tested in genomic DNA, whereas gene fusions (such as ROS1) are usually tested in cDNA [complementary DNA] prepared from RNA. ([Public Summary Document \[PSD\] 1454:3](#))

ESC noted that the current application addressed the main concerns that MSAC had at the time of considering application 1454 – namely, that the current DCAR:

- assessed a small NGS panel test
- included both DNA and RNA testing, or sequential DNA then RNA testing as interventions
- demonstrated that NGS has superior or equivalent analytical performance compared to single-gene assays, or immunohistochemistry (IHC) and fluorescent in situ hybridisation (FISH) testing
- demonstrated that at the proposed items fees, small gene panel testing is associated with superior effectiveness with some small additional costs. ESC considered this to be reasonable.

ESC noted that there were nearly 12,000 new diagnoses of NSCLC in 2021. Standard of care includes sequential testing of gene variants that are mutually exclusive. *EGFR* is tested first; if no variant is identified, testing then moves to *ALK* testing using immunohistochemistry and FISH, then to testing *ROS1*. The current MBS items that support reimbursement of sequential testing are drafted to only support claims under this sequential approach. This application proposed the use of a gene panel to test these variants and also 'beyond restriction' variants (i.e. variants which do not currently have an associated PBS subsidised therapy) including *RET* and *NTRK1*, *NTRK2* and *NTRK3* to expedite testing, and therefore, diagnosis and the start of appropriate targeted therapy.

ESC noted that while the application was restricted to testing for non-squamous non-small cell lung carcinoma, it is comparatively rare for patients with squamous cell carcinoma (SqCC) to

have EGFR mutations. ESC considered that it may be appropriate to extend eligibility to patients with squamous cell carcinoma, noting that SqCC has a number of potentially targetable driver mutations that have not been assessed in this application.

ESC noted that there were multiple therapies available on the Pharmaceutical Benefits Scheme (PBS) targeting each of these variants (although *NTRK* testing in patients with NSCLC is not MBS-reimbursed).

ESC noted the positive feedback from organisations supporting the proposal, but that there was no consumer feedback. Rationale for supporting the application emphasised the benefits of combined testing on one platform over sequential testing. Flexibility of testing could allow more laboratories to provide results sooner to help ensure equity of access. The feedback also noted clinician and patient preference for a single biopsy to provide the sample. ESC considered given the importance of equity of access as a benefit of this testing whether there might be scope to consider in the MBS item descriptor and related specification how to fund access in a way which is equitable for those living in remote and rural communities.

ESC noted that the proposal included three MBS items:

- AAAA – a small gene panel that included DNA and RNA analysis (fee of \$1,247)

OR

- BBBB – a small gene panel that included DNA analysis only (fee of \$682.35)

AND

- CCCC – a small gene panel that included RNA analysis only, and to be done only if BBBB was negative (fee of \$682.35).

ESC discussed the benefits and disadvantages of a combined DNA and RNA panel (item AAAA) compared with sequential DNA and RNA panels (item BBBB, then CCCC). The turnaround time would be faster if running a single panel, leading to more timely diagnosis and therapy initiation, and many clinicians would consider genetic test results before making therapy recommendations. ESC also noted that running a single panel would use less biopsy tissue, which ESC considered to be an important advantage since sample availability may be limited and rebiopsy was not an option for all patients. ESC noted that it was more cost-effective to run a single panel rather than two, but noted that CCCC would only be used if BBBB did not identify any variants. ESC noted the disadvantages of MBS item AAAA included the additional laboratory work for some patients (it would be more challenging to run a single DNA/RNA panel than DNA panel alone which is all that would be needed for more than 50% of patients with simple EGFR or KRAS mutations), that currently not all laboratories will be able to test using the single panel, and that there will be some duplication of work. However, ESC noted that test kit manufacturers may address these challenges in future kit developments.

ESC considered the following amendments to the descriptor to be appropriate:

- The descriptor wording should be “variants”, not “mutations”, to be consistent with other gene testing descriptors on the MBS.
- The specific reference to pembrolizumab for *EGFR*, *ALK* and *ROS1* status should be changed to a more generic PD-(L)1 immunotherapy to help futureproof the MBS item as more therapies are approved.
- The *NTRK* gene is actually three genes, so the descriptor should specify *NTKR1*, *NTKR2* and *NTRK3* to clarify this.

ESC noted the proposed fees and considered them to be appropriate for all proposed item numbers.

ESC noted the comparators (sequential testing of biomarkers) and considered them to be appropriate. Most of these comparators were currently available on the MBS as items 73337, 72846, 73341 and 73344. Testing of *METex14* skipping alterations had been recommended for listing by MSAC. MSAC had recommended that testing for *METex14* skipping (*METex14sk*) alterations be performed without the absence of other NSCLC biomarkers being a prerequisite ([PSD 1660](#)).

ESC agreed that the limit on repeat services for the proposed MBS items was appropriate. ESC agreed that it was appropriate to restrict co-claiming of these comparator item numbers with the proposed MBS item(s) if funded, including restrictions to the existing single-gene items. ESC considered that, if funded, small gene panel testing would likely supersede the comparator item numbers, except MBS item 73351 and therefore the comparator items with the exception of item 73351 should be delisted within a timeframe. ESC noted concerns about the restrictions on comparator item numbers if the gene panels were not available when a patient was first diagnosed. ESC also considered it to be inequitable if patients were to miss out on improved testing due to co-claiming restrictions. Thus, ESC considered that grandfathering these items would be appropriate for a certain timeframe during implementation of the proposed MBS item(s), if they were recommended for funding. ESC suggested that 3 years might be appropriate, as patients who have recurrence after this time would be considered a different diagnosis and would require retesting anyway.

ESC noted that the current sequential testing of biomarkers were currently pathologist-determinable. ESC considered this to be appropriate for the proposed MBS items as well, to facilitate laboratory workflow.

ESC accepted the proposed clinical management algorithms for both options 1 (AAAA) and 2 (BBBB and CCCC).

ESC noted that no studies directly compared the safety of NGS testing with sequential single-gene testing. However, the evidence supported the claim that NGS had a higher proportion of samples being successfully tested (i.e. making more efficient use of the available tissue to get a test result) than sequential single-gene testing, which should correspond to a lower rate of rebiopsy. Steeghs et al. (2022) reported that NGS methods were successful in 97.2% of cases, whereas non-NGS methods were successful in 94.6% of cases¹.

ESC noted that the relationship between insufficient tissue for testing, or test failure due to insufficient DNA or RNA, and subsequent rebiopsy was uncertain, as some international guidelines now recommended the use of liquid biopsy (i.e. using a blood sample) when tumour tissue was insufficient, rather than performing a second biopsy of tumour tissue/cytology. Two case series reported that 13% of patients with insufficient tissue for NGS¹⁶, and 43% of patients with insufficient tissue for testing *EGFR* and *ALK* (by an unspecified method), had a rebiopsy performed¹⁷. The remainder either had plasma NGS or did not have their tumour tested further for biomarkers. ESC noted that there were no Australian guidelines on the role of rebiopsy versus liquid biopsies in the absence of sufficient tissue from the initial biopsy. However, these case series data were unlikely to be relevant to the current Australian setting, as the PBS restrictions for targeted therapies in NSCLC required the biomarkers to be identified in tumour tissue. A higher proportion of failed tests were therefore likely to proceed to rebiopsy than reported in

¹⁶ Li, W, et al. (2021), 'Metastatic NSCLCs With Limited Tissues: How to Effectively Identify Driver Alterations to Guide Targeted Therapy in Chinese Patients', *JTO Clin Res Rep*, vol. 2, no. 5, May, p. 100167.

¹⁷ Gutierrez ME, et al. (2017). Genomic Profiling of Advanced Non-Small Cell Lung Cancer in Community Settings: Gaps and Opportunities. *Clin Lung Cancer*, vol. 18, no. 6, Nov, pp. 651-659.

these case series. ESC noted that there was a risk of additional adverse events with each rebiopsy.

Regarding clinical effectiveness, ESC recalled that a single between-patient study (Steeghs et al 2022) was identified that provided the proportion of samples successfully tested, favouring NGS over sequential single-gene testing (97.2% vs 94.6%).

ESC noted that the Department-contracted assessment report (DCAR) included turnaround time data from three papers, which showed average turnaround-time differences of 0, -1 and -3.15 days in favour of the intervention. There may therefore be additional quality-of-life benefits due to the shorter turnaround time to earlier therapy initiation associated with panel testing. However, ESC noted that many Australian laboratories run these tests once per week, possibly making the DCAR's turnaround time analysis not representative of the real-world Australian setting.

ESC noted that the economic evaluation was a cost-effectiveness analysis. The time horizon for the model was time to first-line treatment decisions. The base case was generated by a modelled stepped analysis, incorporating different aspects of the linked evidence, translations of the clinical evidence, and other key model assumptions separately to distinguish the effect of each of these on the results. Patients entered the model at the point of receiving testing to determine their biomarker status. The model distinguished between patients with advanced disease (or who progress to advanced disease) and those tested at an early disease stage who do not progress to advanced disease. This distinction had been incorporated into the model structure as patients tested early who did not progress incurred the cost of testing, with no benefit in terms of being eligible for targeted therapy. In addition, the cost of current testing differed between these groups, as *ALK* and *ROS1* FISH and *MET*ex14sk testing were restricted to patients with advanced disease (and so would not be incurred by patients diagnosed with early disease who did not develop advanced disease).

ESC noted that uncommon variants that were identified through small gene panel testing methods alone were not assumed to be identified using current test methods. On identification of an actionable variant, patients were assumed to be eligible for targeted therapy. Where an actionable variant was not identified by testing, patients were not eligible for targeted therapy and would receive standard of care treatment. The model assumed that the:

- variants were mutually exclusive
- incremental variants could not be identified by current testing
- patients tested at an early stage of disease and who had insufficient tissue available for testing would only receive a rebiopsy on development of advanced disease. Therefore, rebiopsies were not assumed in those who did not progress to advanced disease. ESC noted that the cost of rebiopsy was high and could affect the outcomes of the model.

As noted previously, *NTRK* testing is currently not MBS reimbursed, so all *NTRK* variants detected by panel testing would be classified as incremental variants. The benefits associated with identifying incremental variants were uncertain as Larotrectinib and Entrectinib were not currently PBS-listed for treatment of adults with NSCLC with *NTRK* variants.

ESC noted an incremental cost-effectiveness ratio (ICER) of \$7,496 per person eligible for targeted therapy. The main driver of the ICER was from the relative outcomes of targeted therapies versus standard of care in those with uncommon actionable variants identified through small gene panel testing only. ESC considered that as some of these uncommon actionable variants might not lead to patients being eligible for a PBS targeted therapy, this might significantly overestimate the benefits of testing. ESC noted that the ICER increased to \$35,862 if benefits from identifying uncommon variants were excluded. However, ESC accepted this

“overestimation”, as new pharmaceuticals were being rapidly developed and this could help to futureproof the model. In the pre-ESC response, the applicant provided an example of an additional *EGFR* variant (*EGFR* exon 20) for which treatments had recently become available.

ESC noted that the DCAR estimated various ICER results to assess the impacts of areas of uncertainty in respect to testing success rates and concordance rates:

- In the stepped analysis an ICER of \$11,352 was reported as arising from base case assumptions of test success rates and concordance rates before the final step of incorporating rebiopsy rates was taken into account.
- An ICER of \$12,662 resulted if both the comparator and intervention arms were assumed to have an identical success rate of 97.2% (which was the success rate reported in the literature for NGS).
- Various assumptions on concordance rates generated an ICER as low as \$4509 to as high as \$18,168.

ESC noted that because the economic model was truncated at the point of treatment it did not model changes in treatment and therefore changes in health outcomes arising from the panel test. This meant it omitted the following impacts which would have favoured gene panel testing (and might therefore be conservative in its approach):

- Reduced testing turnaround time which, as previously noted, might generate additional quality-of-life benefits due to earlier therapy initiation. However, as also previously noted, it was unclear how representative of real world settings the DCAR estimated shorter turnaround times would be.
- Reduced adverse events due to reduced rate of rebiopsy.
- Health benefits from not missing out on targeted treatment due to insufficient material for rebiopsy.

ESC noted that the financial impact was calculated using a market-share approach that assumed 100% replacement of single-gene tests. ESC noted that the assumption in the financial modelling of some expansion of laboratory capacity to facilitate small gene panels appeared reasonable. The DCAR estimated a net financial impact to the MBS of \$1.47 million in calendar year 2023 (year 1) to \$2.28 million in calendar year 2026 (year 6). ESC noted that the cost of small panel testing varied depending on the approach employed and the inpatient/outpatient split (assumed to be 31.8% inpatient, 68.2% outpatient). In its pre-ESC response, the applicant stated that it did not anticipate any cost shifting from state to federal governments. In addition, ESC noted that the financial impact estimates might be conservative because:

- evidence from applications [1161](#) and [1173](#) demonstrated lower-than-expected MBS utilisation
- there might be additional small cost savings in the reduction of *METsk* testing, as this was associated with additional consultation (applicant estimated \$139,691); ESC queried whether this was reasonable, as the amount of additional specialist consultation *METsk* testing required was uncertain.
- if core needle biopsies were used for rebiopsy, there would be additional cost savings (associated with hospital admission) if panel testing was introduced.

17. Applicant comments on MSAC’s Public Summary Document

The College and Fellows have nil comments to make on the PSD for Application 1721. The College’s Working Party would like to express their delight in MSAC approving public funding of biomarker testing for patients with NSCLC, and would like to take this opportunity to thank the Department for its assistance throughout the assessment process.

18. Further information on MSAC

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