Australian Government

Department of Health

Ratified
PICO Confirmation

Application 1634

Comprehensive genomic profiling of non-squamous non-small cell lung cancer tumour tissue specimens using next generation sequencing assays

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	Patients with non-squamous (or histology not otherwise specified) non-small cell lung cancer (NSCLC)
Prior tests	Disease staging and histology workup. This is part of routine management and there would be no change between the intervention and comparator
Intervention	Comprehensive genomic profiling (CGP) using a next generation sequencing (NGS) assay to simultaneously test for relevant variants in the following genes: *EGFR*, *ALK*, and *ROS1*
Comparator	Testing for activating mutations in the *EGFR* gene, ALK IHC and ROS1 IHC, with subsequent *ALK* FISH or *ROS1* FISH as appropriate
Evidentiary standards	*EGFR* cobas® real time PCR test *ALK* FISH *ROS1* FISH
Outcomes	*Test outcomes* *Efficacy/effectiveness* Positive percent agreement and negative percent agreement of NGS assays against the evidentiary standards Positive predictive value and negative predictive value of NGS assays against the evidentiary standards Concordance between NGS assays and comparator biomarker assays Concordance between FoundationOne CDx and NGS assays expected to be used in Australia Test turnaround time *Safety outcomes* Rebiopsy rate / test failure rate / inadequate sample rate (e.g. from an inadequate cytological specimen) Harms from rebiopsy *Treatment outcomes* *Effectiveness* Direct health outcomes (survival/mortality) Health outcomes resulting from false positives and false negatives of any of the proposed NGS assays against each of the evidentiary standards Health outcome changes based on increase in number of patients eligible for PBS-listed targeted therapies and/or earlier commencement of treatment *Healthcare resources* Cost Cost-effectiveness Net Australian Government healthcare costs

ALK = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; FISH = fluorescence *in situ* hybridization; IHC = immunohistochemistry; *ROS1* = ROS proto-oncogene 1

PPICO rationale for investigative medical services

Population

The population of interest for testing comprises patients with non-squamous (or not otherwise specified) non-small cell lung cancer (NSCLC). When these patients are also stage IIIB (locally advanced) or stage IV (metastatic), they can be considered for treatment with Pharmaceutical Benefits Scheme (PBS)-listed tyrosine kinase inhibitors (TKIs).

PASC noted that, consistent with the existing Medical Benefits Scheme (MBS) item for EGFR testing, the proposed population for the intervention is not restricted by stage of disease.

Most patients will progress to having locally advanced or metastatic disease, if they do not already, at the time of diagnosis, so most test results will be relevant to decisions regarding subsequent codependent treatments.

Patients with early stage lung cancer may be managed by surgical resection of the tumour. However, in locally advanced or metastatic cancer where surgical resection is no longer curative due to the spread of the tumour, systemic therapy is recommended. The choice of systemic therapy is increasingly being made using identification of the molecular biomarkers in a patient's tumour.

There are two different methods of estimating the size of the population of interest for testing, which result in similar estimates. The epidemiology-based approach suggests that of 12,990 new cases of lung cancer diagnosed in Australia in 2020, non-small cell lung cancer accounts for 86.6% (DoH 2019). Therefore, there is an estimated 11,249 incident cases of NSCLC diagnosed in 2020, of which 8,696 (77.3%) are stage III or IV (DoH 2019). Of these, assumptions previously accepted by PBAC were that 63.3% of NSCLC patients have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 and are eligible for PBS-listed treatment, and 85% of patients opt for treatment (DoH 2019). This results in an estimated 4,679 patients for 2020 who would be eligible and potentially be tested for systemic therapy (8,696* 63.3% * 85%). This population is relevant for aspects of the comparator, as confirmatory FISH testing for *ALK* and *ROS1* may only occur at stage III or IV NSCLC.

The second method of determining the size of the population, is using the market based approach, derived from the number of times that *EGFR* variant testing has been performed using MBS item 73337 (the first step of the comparative test strategy). This number relies on the tumour being able to be biopsied, and for the patient to be treated within the private healthcare sector or as a privately funded patient in the public sector. In 2019-20, there were 4,643 MBS services claimed under MBS item 73337 for the testing of *EGFR* variants. As some patients may have used the MBS item more than once, the number of patients who were tested and billed using this MBS item would be slightly fewer than 4,643.

The frequency of *EGFR*, *ALK* and *ROS1* variants (as determined by the evidentiary standards) are reported in Table 1.

Table 1 Prevalence of *EGFR*, *ALK* and *ROS1* variants in the Australian NSCLC population

Gene alteration	Prevalence	Reference
EGFR activating pathological variants	15%	MSAC application 1161 (MSAC 2012)
ALK rearrangements	3.0%	MSAC application 1250.1 (MSAC 2014)
ROS1 rearrangements	1.2%	MSAC application 1454 (MSAC 2018)

ALK = anaplastic lymphoma kinase gene; *EGFR* = epidermal growth factor receptor gene; *ROS1* = ROS1 receptor tyrosine kinase gene

Rationale

Next generation sequencing (NGS) assays may be used to identify molecular alterations in DNA and RNA from multiple tumour types. An alternative population could therefore have been any patient with a solid tumour that could be targeted by a PBS-listed drug (i.e. NSCLC, melanoma, breast cancer, colorectal cancer, ovarian cancer, prostate cancer). However, in a meeting held 29 May 2018 with representatives from the Department of Health, it was suggested to the applicants that any MSAC application would benefit from focusing on a discrete population. NSCLC was chosen as an appropriate, high-need discrete patient population as there are multiple biomarker tests associated with the identification of multiple treatments listed on the PBS or under active clinical development. The applicants state that the use of an NGS assay outside of the NSCLC population will be the basis of future MSAC applications.

Prior tests

Prior testing, common to the intervention and comparator groups, would be performed to define the population. Guidelines for the management of NSCLC suggest the following procedures: physical examination and assessment of medical history; complete blood count; renal and liver function testing; pathologic evaluation of tumour biopsy specimen to determine histological subtype (e.g. squamous or non-squamous); contrast-enhanced computed tomography (CT) scan of the chest and upper abdomen; and a potential further fluorodeoxyglucose positron emission tomography (FDG-PET) scan if the presence of metastatic disease is suspected after CT scan (equivocal CT scan result). If the patient has locally advanced or metastatic disease unsuitable for conservative management or surgical resection, the use of systemic treatment is recommended. In order to determine eligibility for targeted therapies, molecular testing of the patient's tumour tissue is performed (NCCN 2019; Planchard et al. 2018).

Intervention

The intervention is comprehensive genomic profiling (CGP) using an NGS assay to identify molecular alterations in DNA or RNA arising in a tumour tissue sample in patients with NSCLC.

PASC advised that cytology specimens should be considered tumour tissue if there is tumour visible on the slide, and a pathologist confirms there is adequate material available for analysis.

The purpose is to determine suitability for first-line treatments in advanced NSCLC. The variants currently 'clinically actionable' to be reported on for codependent medicines are *EGFR* activating mutations, and *ALK* and *ROS1* gene rearrangements.

The steps involved are:

- Isolation of tumour DNA and RNA from tumour tissue specimen
- Preparation of sequencing libraries
- Enrichment of sequencing libraries for genes of interest
- Sequencing of enriched libraries
- Analysis and reporting of test results.

Some laboratory components of CGP using NGS assays can be performed on multiple tumour specimens at the same time, benefiting from 'batch processing' and/or automation of processing of samples. However, the preparation of a test report outlining the clinically actionable results must be done on a per patient basis.

The NGS assays proposed in the application have the ability to identify four classes of genomic alterations: base substitutions (single nucleotide variants); insertions and deletions; copy number alterations and gene fusions (rearrangements). It is also able to provide information on genomic signatures including tumour mutation burden (TMB) and microsatellite instability (MSI).

It is proposed that any NGS assay covering the nominated genes with appropriate regulatory approval as an *in vitro* companion diagnostic in NSCLC could be used under the proposed MBS item. Some of the evidence linking the NGS assay to clinical utility that will be provided in the submission is based on the FoundationOne® CDx, which is not currently used in Australia. The Applicant Developed Assessment Report will therefore also need to compare the test performance of assays most likely to be used in Australia against the FoundationOne® CDx. The applicants understand that platforms manufactured by Illumina such as NextSeq™ 500/550/550Dx instruments are the most commonly used NGS platforms in Australian laboratories. Current manufacturers of NGS assays include Roche Diagnostics, Illumina and Thermo Fisher.

PASC sought confirmation that the range of genomic profiling tests available are capable of detecting ALK and ROS1 gene rearrangements, and also of differentiating EGFR activating mutations and ALK and ROS1 gene rearrangements from other pathogenic variants of these genes.

The intervention is proposed to be 'treatment agnostic', i.e. the results of the testing may be used to identify patients eligible to access all targeted treatments currently listed on the PBS for the treatment of NSCLC. Targeted therapies currently listed on the PBS for patients with locally advanced or metastatic NSCLC are shown below in

Table 2. It would also be possible to include biomarkers where the detection of a genetic variant indicates that a patient should not receive a certain treatment. Testing for *EGFR* T790M variants (under MBS item 73351) subsequent to disease progression while on EGFR-targeted therapies would still occur to determine if new resistance-variants develop.

Table 2 List of biomarker-specific therapies currently available through the PBS

Biomarker	PBS therapy	PBS code(s)	Sponsor
EGFR activating mutation positive	Erlotinib	10014C; 10019H; 10020J; 10025P; 10028T; 11259N; 11260P; 11263T	Roche
	Gefitinib	11264W; 8769M	Astra Zeneca
	Afatinib	11329G; 11335N; 11336P; 11341X; 113147F; 11348G; 11359W	Boehringer Ingelheim
	Osimertinib (first-line)	Recommended by PBAC	Astra Zeneca
EGFR T790M mutation positive after prior EGFR targeted treatment	Osimertinib (second-line)	11620N; 11622Q	Astra Zeneca
ALK gene rearrangement positive	Crizotinib	10322G; 10323H	Pfizer
	Ceritinib	11056X	Novartis
	Alectinib	11226W	Roche
	Brigatinib	11980M; 11974F; 11976H; 11984R	Takeda
	Lorlatinib (second-line)	12096P; 12091J	Pfizer
ROS1 gene rearrangement positive	Crizotinib	11589Y; 11594F	Pfizer
	Entrectinib[a]	12092K	Roche

ALK = anaplastic lymphoma kinase gene; *EGFR* = epidermal growth factor receptor gene; *ROS1* = ROS1 receptor tyrosine kinase gene

Source: MSAC 1634 application form page 5 (updated with recent PBAC listings)

Currently, the PBS restrictions for most of the therapies targeting *ALK* or *ROS1* gene rearrangements (all except second-line lorlatinib) specify the method of determining the variants in order for the patient to be eligible for the therapeutics (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 MBS item for CGP is listed on the MBS, revisions to the restrictions listed on the PBS would be required to allow for either FISH or NGS in the criteria for crizotinib, ceritinib, alectinib, and entrectinib.

Many of the commercially available NGS assays are also able to detect biomarkers such as *BRAF*, *RET*, *NTRK* and *MET* using the same tumour tissue and at the same time as relevant *EGFR*, *ALK* and *ROS1* alterations. The proposed MBS item descriptor nominates the biomarkers to be reported on, but it is expected that only minor changes would be required to amend the descriptor for further biomarkers and targeted therapies under clinical development.

PASC noted that the applicants foreshadowed that additional biomarkers to be reported on in the near future under the requested MBS item could include MET exon 14 skipping alterations, and NTRK1, NTRK2, NTRK3 and KRAS G12C variants. PASC advised that, for test reporting purposes, the evidentiary standard tests in the trials of the related medicines should be used to identify the specific biomarkers in each case.

Appropriate reimbursement for CGP of patients with NSCLC is not currently listed on the MBS, although the applicants understand that some small NGS panels are routinely used in clinical practice and claimed under the single gene MBS items (e.g. MBS item 73337 for *EGFR* variant testing).

Some lung cancer patients would currently be having NGS analysis of their tumour in a research setting, under the Australian Genomics Lung Cancer Flagship (using whole exome sequencing and whole genome sequencing) (Australian Genomics Health Alliance).

The current turnaround time for CGP using a NGS assay between receipt of a patient tumour specimen at the pathology laboratory and availability of results is believed to be 10-12 days, although the applicants acknowledge that the optimal turnaround time is 5 days.

Pathologist advice provided during the development of MSAC application 1495 suggested that the proportion of samples required to be referred to another laboratory for CGP using an NGS would be higher than with the use of the comparator tests (which most laboratories can perform). An additional specimen retrieval fee (MBS item 73940, $10.25) would therefore be required for a proportion of patients.

PASC considered that equity of access to the requested testing and subsequent treatment should not be a particular concern.

PASC noted that there may initially be capacity issues for laboratories potentially requiring samples to be referred, but laboratory capacity will expand naturally with market forces over the next couple of years.

Registration status with the Therapeutic Goods Administration (TGA)

There are currently no NGS assays approved by the TGA for the purpose of detecting biomarkers for targeted treatment of patients with NSCLC.

It is anticipated that the forthcoming CGP assay based on the FoundationOne® CDx assay will seek TGA-approval as an *in vitro* Diagnostic (IVD) companion diagnostic with indications consistent with the FDA-approved indications for FoundationOne® CDx.

Foundation Medicine and Roche Sequencing Solutions (Roche Diagnostics) are developing a NGS CGP panel based on the FoundationOne® CDx assay that will enable laboratories to perform CGP locally.

There are several NGS assays available in Australia for use in patients with NSCLC, marked as 'Research Use Only' (RUO): (AVENIO tumor tissue targeted panel (17 genes), AVENIO tumor tissue expanded panel (77 genes), TruSight Oncology 170 (170 genes) and TruSight Oncology 500 (523 genes from DNA and RNA). The applicants suggest that local laboratories will be able to purchase RUO products from commercial suppliers and develop an IVD test under the framework of the 'Requirement for the development of an in-house *in vitro* diagnostic medical devices (IVDs) (Fourth Edition 2018)'.

Rationale

NTRK testing of solid tumours to identify patients eligible for larotrectinib and microsatellite instability/DNA mismatch repair (MSI/MMR) testing to identify patients eligible for pembrolizumab may be included on some NGS panels, but are considered to be outside the scope of testing patients with NSCLC. The decision not to include *NTRK* fusions is consistent with what has been recommended by the ESMO Precision Medicine Working group (Mosele et al. 2020).

No mention has been made in the application form of circulating tumour DNA or plasma-based DNA. These would be considered outside of scope.

Although CGP using a NGS assay may also be performed for the purposes of monitoring of treatment response, this is outside the scope of the current assessment.

Comparator

The comparator to CGP using an NGS assay is the use of sequential testing of biomarkers for targeted therapies for NSCLC using items currently available on the MBS. Specifically, this is:

- Testing of *EGFR* activating mutation status (MBS item 73337)
- Immunohistochemistry (IHC) testing as triage ALK testing and triage ROS1 testing (most likely included under MBS items 72847 or 72849 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)

PASC confirmed that the comparator to CGP was separate testing of EGFR for activating mutations, IHC testing for ALK and ROS1, and possible subsequent testing for ALK gene rearrangements and/or ROS1 gene rearrangements using FISH.

The clinical management algorithm shown in Figure 1 shows the flow of how the results of the earlier tests influence whether subsequent testing is performed. Currently, patients initially diagnosed with NSCLC are tested for *EGFR* variants and IHC triage testing after exclusion of squamous NSCLC.

PASC advised that IHC triage testing for ALK and ROS1 normally occurs at the point of diagnosis, with reference to MBS items 72847 or 72849, although IHC coning rules mean these tests may not attract additional reimbursement.

If patients are *EGFR* activating mutation negative, but positive or equivocal on ALK IHC triage testing (staining intensity score >0), they may receive *ALK* gene rearrangement confirmatory testing using FISH if/when they have locally advanced or metastatic disease.

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

If patients are not locally advanced or metastatic 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 current use of MBS items for sequential testing from MBS statistics is shown in Table 3.

It is expected that the proposed intervention would likely replace sequential testing of different biomarkers in patients with NSCLC. It is expected that all patients who undergo *EGFR* testing would also undergo triage testing for ALK and ROS expression, under an IHC item such as 72847 (for 4-6 antibodies) or 72849 (for 7-10 antibodies). Only those positive on IHC testing and who progress to being locally advanced or metastatic would be eligible to undergo *ALK* or *ROS1* FISH testing (*ALK* =

anaplastic lymphoma kinase gene; *EGFR* = epidermal growth factor receptor gene; FISH = fluorescence *in situ* hybridization; *ROS1* = ROS1 receptor tyrosine kinase gene

Table 4).

PASC considered that the consequences of funding the proposed comprehensive genomic profiling for the costs of the expected reduced IHC testing for ALK and ROS1 would not be straightforward to estimate. Although these IHC items are likely to be eligible for MBS items 72847 or 72849, for many patients tested these items may also be coned out under MBS rules.

The consequence might be billing of a cheaper MBS item for fewer IHC antibodies (i.e. without the antibodies for ALK or ROS1) if not coned out, or no cost consequence at all if the IHC item would otherwise have been coned out.

Table 3 MBS statistics on use of comparator MBS items

MBS item and use	16/17	17/18	18/19	19/20
MBS item 73337 *EGFR*	3,695	3,912	4,371	4,643
MBS item 73341 *ALK* FISH	258	353	165	221
MBS item 73344 *ROS1* FISH	-	-	26	247

ALK = anaplastic lymphoma kinase gene; *EGFR* = epidermal growth factor receptor gene; FISH = fluorescence *in situ* hybridization; *ROS1* = ROS1 receptor tyrosine kinase gene

Table 4 Sequential testing diagnosis of *EGFR*, *ALK* and *ROS1* variants in NSCLC patients from July 2019 to June 2020

Test eligibility for NSCLC patients	*EGFR* (Item 73337)	*ALK* FISH (Item 73341)	*ROS1* FISH (Item 73344)
Number tested	4,643[a]	221[a]	247[a]
Number likely negative	3,947 (85%)[b]	57 (26%)[c]	208 (84.3%)[d]
Number likely positive	696 (15%)[b]	164 (74%)[c]	39 (15.7%)[d]

ALK = anaplastic lymphoma kinase gene; *EGFR* = epidermal growth factor receptor gene; FISH = fluorescence *in situ* hybridisation; NOS = not otherwise specified; NSCLC = non-small-cell lung cancer; *ROS1* = ROS1 receptor tyrosine kinase gene

[a] Based on Medicare statistics for Items 73337 and 73341 requests for July 2019 to June 2020.

[b] Based on prevalence data for *EGFR* non-squamous NSCLC or NOS (MSAC 2012).

[c] Based on a sensitivity of ALK IHC of 100%, a specificity of ALK IHC of 95% and prevalence of ALK of 3% (MSAC 2014), with FISH as the reference standard, the positive predictive value of ALK IHC (74%) is the proportion positive on FISH after testing positive on IHC.

[d] Based on a sensitivity of ROS1 IHC of 95.1%, a specificity of ROS1 IHC of 93.8% and prevalence of ROS1 of 1.2% (MSAC 2018), with FISH as the reference standard, the positive predictive value of ROS1 IHC (15.7%) is the proportion positive on FISH after testing positive on IHC.

The MBS items relevant to the comparator are summarised below.

Table 5 Relevant MBS items for the comparator

Category 6 – PATHOLOGY SERVICES	Group P7 - Genetics
72847 Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 4-6 antibodies **Fee:** $89.40 **Benefit:** 75% = $67.05 85% = $76.00	
72849 Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 7-10 antibodies **Fee**: $104.30 **Benefit**: 75% = $78.25 85% = $88.70	
73337 A 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 determine if the requirements relating to epidermal growth factor receptor (*EGFR*) gene status for access to erlotinib, gefitinib or afatinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. **Fee:** $397.35 **Benefit:** 75% = $298.05 85% = $337.75	
73341 Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with 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 if requirements relating to *ALK* gene rearrangement status for access to an anaplastic lymphoma kinase inhibitor under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. **Fee:** $400.00 **Benefit:** 75% = $300.00 85% = $340.00	
73344 Fluorescence in situ hybridization (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small-cell lung cancer (NSCLC), 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 if requirements relating to *ROS1* gene rearrangement status for access to crizotinib or entrectinib under the Pharmaceutical Benefits Scheme are fulfilled. **Fee:** $400.00 **Benefit:** 75% = $300.00 85% = $340.00	
72860 Retrieval and review of one or more archived formalin fixed paraffin embedded blocks to determine the appropriate samples for the purpose of conducting genetic testing, other than: (a) a service associated with a service to which item 72858 or 72859 applies; or (b) a service associated with, and rendered in the same patient episode as, a service to which an item in Group P5, P6, P10 or P11 applies Applicable not more than once in a patient episode Fee: $85.00 Benefit: 75% = $63.75 85% = $72.25	

The cost of sequential testing would differ depending on how sequential testing is conducted with regards to the timing of the tests, whether a specialist attendance is required to request FISH tests and the proportion of tests that get referred for central laboratory testing.

Not all tumour samples are sufficient to be able to determine the presence or absence of biomarkers. Yu et al. (2018) reported that as the number of single-gene tests ordered increased, a reduction in the proportion of samples that could complete each additional test was observed, in NSCLC patients. This study observed that 11.6% of samples were insufficient to have a single-gene test completed, which is consistent with previous MSAC advice that suggested that 12% of patients would require a rebiopsy (MSAC Application 1161, November 2012). When two or three single-gene tests were requested (such as for ALK and ROS1 testing), the proportion of samples that could not complete the requested number of tests increased to 15% and 22.9%, respectively.

PASC advised that the proportion of samples that were insufficient for testing reported by Yu et al. (2018) was likely an overestimate because Australian practice has already optimised sample collection and handling.

PASC noted that the applicants requested that near market comparators of MET exon 14 skipping alterations, and NTRK1, NTRK2, NTRK3 and KRAS G12C variants be incorporated into the list of eligible comparators. PASC considered that it would be necessary to identify the related evidentiary standards from the studies of the related codependent medicines to be considered by PBAC, and to extend the related comparative analytical performance assessments to include these additional biomarkers.

PASC advised that the near market comparators should not be included as part of the base case for the economics and financial analyses, but may be considered as part of their sensitivity analyses. This will require the applicants to make a judgement call regarding what the near market comparator costs would likely to be.

Outcomes

Patient relevant

Safety: One of the clinical claims is that a benefit of simultaneous testing using an NGS assay is the smaller amount of total tumour tissue required than sequential testing for individual biomarkers. The outcomes of interest for safety are therefore the rate of rebiopsy and adverse events associated with the rebiopsy procedure in each arm.

As a proxy for rebiopsy rate, test failure rate and inadequate sample rate should also be reported.

Clinical effectiveness:

Any direct evidence available comparing the health outcomes (overall survival/ mortality) of patients tested with an NGS assay versus the comparator sequential testing should be reported.

Preliminary evidence presented in the application form suggests that NGS is more sensitive at detecting the biomarkers than alternative testing methodologies (Schrock et al. 2016; Ali et al. 2016, Lin et al. 2019).

PASC considered that it would be important to assess the applicability of these studies to the Australian setting, where there is IHC triage for ALK and ROS1 and not just FISH testing. PASC noted that ALK FISH is a complex assay due to the small split apart of signal, and that there could be false negatives if IHC was not also considered.

The hypothesis is that the additional patients identified would benefit from receiving targeted therapy, rather than immunotherapy ± chemotherapy.

The applicants will therefore be required to present the results of:

- Positive percent agreement and negative percent agreement (akin to the concepts of sensitivity and specificity) of the NGS assays, compared against the evidentiary standards; (the tests used in the key trials that established the clinical utility of the targeted therapies);
- Positive predictive value and negative predictive value of the NGS assays, compared against the evidentiary standards;
- Concordance between NGS assays and the comparator tests (if different from the evidentiary standards), and
- Concordance between NGS assays (i.e. concordance between the FoundationOne® CDx and the assays expected to be used in Australia).

Furthermore, the clinical impact of the discordant results should be examined to establish the:

- Effectiveness of targeted treatment in the additional patients identified as suitable for NGS, compared to immunotherapy ± chemotherapy; and
- Effectiveness of the targeted treatment in the additional patients identified as suitable for NGS, compared to patients receiving targeted treatments after being identified using comparator biomarker tests.

PASC considered that if a positive biomarker as defined for PBS eligibility is detected by one assay, then the same clinical response can be expected as if it were detected by any other assay, and therefore the second point above relates primarily to the sensitivity of the different assays.

PASC noted that in order to establish the comparative effectiveness of testing, the clinical consequences of discordant results should be considered. For example, in patients identified as suitable for targeted treatment by CGP and not through the current testing strategy, it is possible that treatment would be as effective as it is in those identified through the current testing strategy. However, if any estimate of treatment effectiveness in the discordant groups is not established with evidence, it will need to be assumed, and this assumption should be explicit.

PASC noted that where discordant results are found for the biomarkers as defined, in general, it is reasonable to assume in favour of CGP. Further consideration will need to be given to where CGP identifies pathogenic variants in the relevant genes beyond those currently defined as the biomarker.

PASC considered that "turnaround time" was a relevant outcome to include.

Healthcare system

Cost of testing and any associated rebiopsies

Cost-effectiveness of testing and downstream implications

Financial implications.

Current clinical management algorithm for identified population

PASC advised that IHC triage testing of ALK and ROS1 occur at the point of diagnosis (at the same time as EGFR testing).

The clinical management algorithms required amending post-PASC. The current clinical management algorithm showing testing via multiple MBS items is shown in Figure 1.

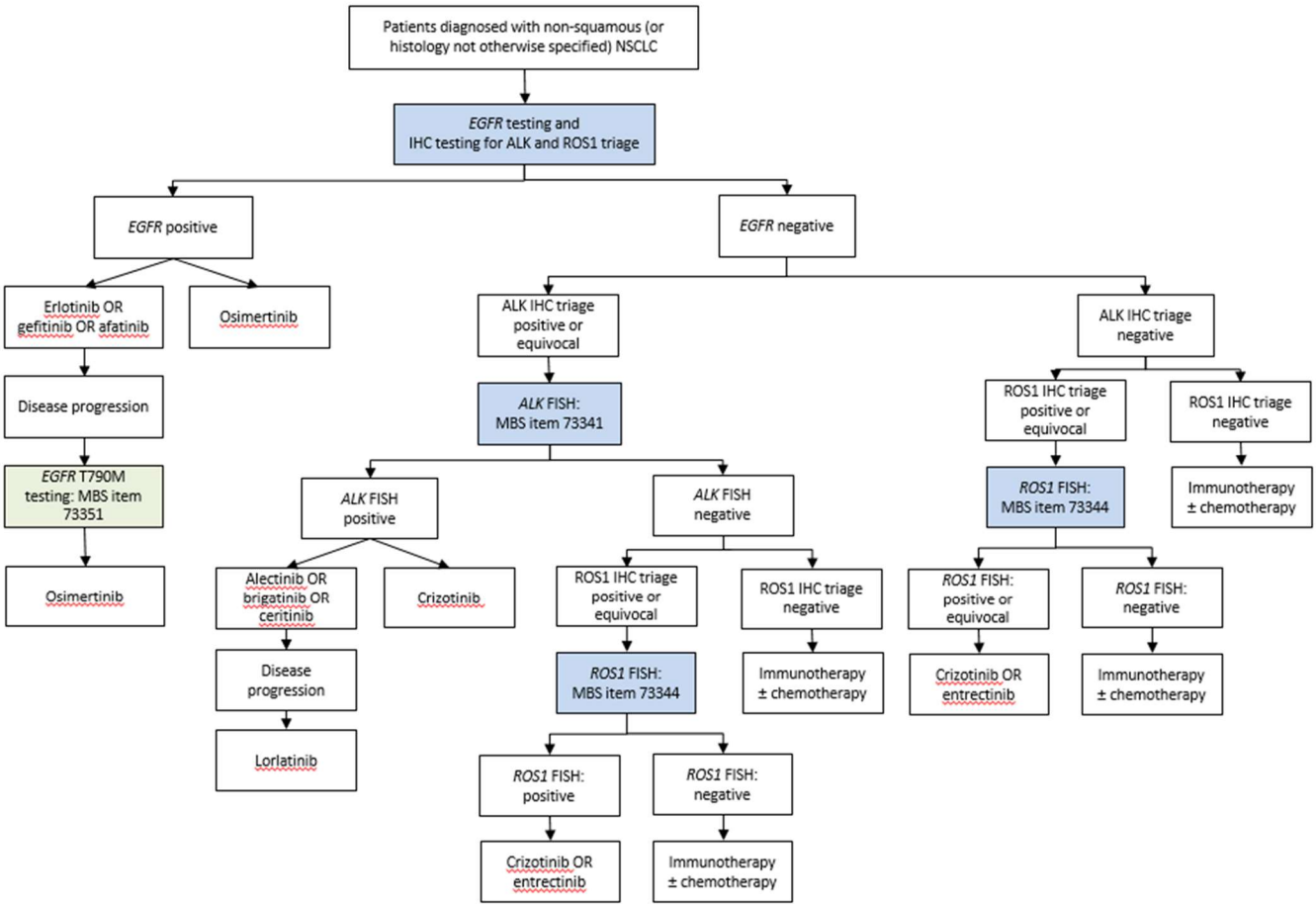

Figure 1 Current clinical management algorithm showing sequential molecular biomarker testing strategy

Note: The comparator tests to be replaced are shown in blue. Testing for *EGFR* T790M variants using MBS item 73351 is unlikely to alter.

Proposed clinical management algorithm for identified population

The proposed clinical management algorithm (restricted to therapies currently available through the PBS) is shown in Figure 2. The management options and downstream services are identical to the current clinical management algorithm. However, there may be a reduction in the number of procedures required to obtain further biopsy material in the situation where the original tissue sample is depleted.

Preliminary evidence suggests that CGP using a NGS assay is more sensitive than current single-biomarker tests, which may result in more people becoming eligible for targeted therapies. Further, patients without *EGFR* variants may have a shorter time between testing and treatment if the biomarkers are tested simultaneously, than they would if the biomarkers are tested sequentially.

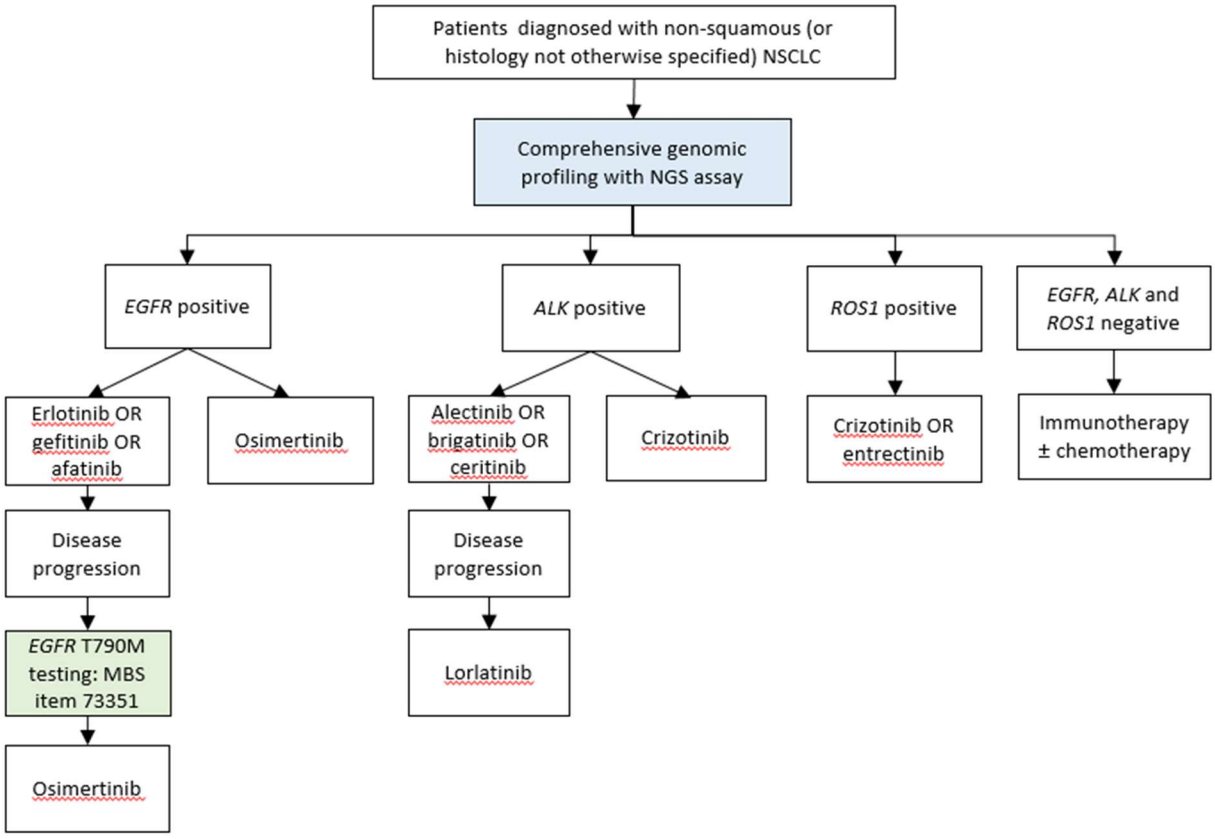

Figure 2 Proposed clinical management algorithm showing CGP with an NGS assay

Note: The intervention is shown in blue. Testing for *EGFR* T790M variants using MBS item 73351 is unlikely to alter.

Proposed economic evaluation

The applicants expected that the evidence presented in the ADAR would support a claim that CGP using a NGS assay has *at least non-inferior*, and potentially superior effectiveness, in identifying genomic alterations used to inform subsequent clinical management decisions for patients with stage IIIB or IV NSCLC compared with the use of sequential molecular biomarker tests currently listed on the MBS. The assumption to be examined if claiming superiority, is that superior sensitivity at identifying patients eligible for treatment, and/or the reduced turnaround time between testing and diagnosis will result in superior health outcomes.

The claim is also that CPG using an NGS assay has at least non-inferior safety (and potentially superior safety) to sequential testing under the current MBS items.

If the evidence presented demonstrates non-inferior effectiveness and safety, the appropriate economic evaluation would be a cost-minimisation analysis (Table 6) or cost consequences (such as additional cost per patient receiving targeted therapy). If evidence is identified that safety and/or effectiveness is superior, then a cost-effectiveness or cost-utility analysis is recommended (Table 6).

PASC suggested that near market comparators could be included in sensitivity analyses in the economic and financial analyses.

Table 6 Classification of the comparative effectiveness and safety of the proposed intervention compared with its main comparator and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Non-inferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Non-inferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

[b] An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence

Proposed item descriptor

Table 7 shows a potential MBS item descriptor for testing for biomarkers within patients with NSCLC.

PASC supported the proposal that CGP of tumour tissue using a NGS assay would be performed once for each diagnosis of NSCLC, and advised that this should be included in the proposed item descriptor to avoid repeat testing for monitoring purposes, which would need to be the subject of another application.

The applicant considered that, for most patients, testing for genomic alterations would be performed at the time they would otherwise be eligible for systemic therapy (i.e. when they have locally advanced or metastatic disease). However, in some cases, testing of NSCLC tumour tissue would be requested for patients at the time of diagnosis with early-stage disease (not amenable to systemic therapy), in order to avoid delays, costs and safety issues with collection of a second biopsy specimen at the point of disease progression.

PASC suggested that, in most cases, NGS testing would be organised at the time of diagnosis (as EGFR testing is currently), to avoid issues such as block retrieval and re-cutting.

Table 7 Applicant proposed MBS item descriptor

Category 6 – Pathology Services
Comprehensive genomic profiling using a next generation sequencing assay performed on 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 consulting physician, to determine if the eligibility requirements relating to biomarker status for access to targeted treatments under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $ to be confirmed

Explanatory notes:

1. This item cannot be claimed in addition to MBS items 73337, 73341 or 73344.
2. The assay must be appropriate for detecting variants in the:
    a. Epidermal growth factor receptor (*EGFR*) gene (activating variants would allow access to erlotinib, gefitinib, afatinib or osimertinib);
    b. Anaplastic lymphoma kinase (*ALK*) gene (rearrangements would allow access to crizotinib, ceritinib, alectinib or brigatinib);
    c. C-ROS proto-oncogene 1 (*ROS1*) gene (rearrangement would allow access to crizotinib or entrectinib).

PASC supported an item descriptor that did not define a specific genomic sequencing methodology. PASC noted that there is no precedent for listing genes in the explanatory notes, and advised that the appropriateness of requiring the MBS item descriptor or explanatory notes describe the minimum set of genes that should be included in a test to be eligible under an MBS item would need to be considered further by MSAC.

PASC considered that the reporting of variants, which did not relate to the eligibility criterion for a PBS-subsidised medicine (for example to suggest eligibility for a medicine that is not subsidised on the PBS for NSCLC) raised issues which would need further consideration by the applicant and MSAC, accepting that such expanded reporting may already be occurring with privately funded panel testing.

PASC advised that the proposed MBS item should be pathologist determinable, to be consistent with EGFR testing.

PASC noted that the proposed item is not to be co-claimed with tests for EGFR, ALK or ROS1 FISH (MBS items 73337, 73341 or 73344), and questioned whether this limitation should be reinforced in the item descriptor rather than being left in the explanatory notes. Some patients may have claimed one (but not all) of these items, which may initially lead to those patients who have been partially tested under existing items being disadvantaged.

The applicants committed to determining an MBS fee as part of preparing the Applicant Developed Assessment Report for consideration by MSAC. The price of the CGP kit will be different to the fee, as the fee must incorporate other components required to deliver the service. The analysis and reporting of CGP results requires a significant amount of time and expertise, contributing to an increase in the cost of NGS testing over single gene testing currently funded through the MBS.

The applicants provided a comparison of the NGS assays currently marketed in Australia, including their fees and what is included (Table 8). The applicants were requested to confirm whether the tests listed are suitable for testing both *ALK* and *ROS1.*

Table 8 Comparison of CGP assays currently marketed in Australia

	Roche Foundation Medicine F1CDx (send out)	Roche AVENIO/F1 (RUO) CGP kit	Illumina TruSight Oncology 500 (TSO500)	ThermoFisher Scientific Oncomine Plus
Coverage	324 genes	324 genes	523 genes	>500 genes
DNA and/or RNA	DNA only	DNA only	DNA and DNA/RNA options	DNA and RNA
Turnaround time[a]	5 days	5 days	5 days	3 days
List price/sample tested	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
Inclusions in price	All stages from sample to clinical reporting (wet lab, secondary analysis and tertiary analysis) including costs associated with consumables/reagents, full time equivalent (FTE) staff, analyses software and data storage	Assay kit and sequencing consumables, costs associated with nucleic acids extraction and secondary analysis	Assay kit and sequencing consumables only.	Assay kit, sequencing consumables and tertiary analysis.
Exclusion in price	None (complete end-to-end)	Costs associated with tertiary analysis software (clinical reporting), data storage and FTE staff for wet lab workflow	Costs associated with nucleic acids extraction, tertiary analysis software (clinical reporting), data storage and FTE staff for wet lab workflow	Costs associated with nucleic acids extraction, data storage and FTE staff for wet lab

[a]from sample to report but dependent on laboratory workflow; shaded cells are not publicly available, and estimates are based on feedback the applicants obtained from clinical experts. The applicants therefore considered these prices to be confidential, and thus to be redacted from the PICO confirmation prior to the document being made publicly available.

Source: Roche (2021) 'Meeting with the Department of Health Briefing Document'.

Consultation feedback

PASC noted that a professional group was supportive of the application, and that the Australia-wide "ASPiRATION" trial was due to commence early 2021 to assess the clinical impact of CGP in metastatic lung cancer patients.

PASC noted that positive feedback was received from a genomic testing group.

PASC noted that feedback from a clinical society was supportive of the application, noting the benefits of reduced sample processing and reduced need for rebiopsy. The society suggested that the MBS item be "future-proofed" for biomarkers in development, and that having an MBS item for CGP would improve equity of access to the technology, and that multidisciplinary teams should be required to consider the results of the CGP.

PASC advised that the proposal, received as part of public consultation, to remove the term "comprehensive genomic profiling" was unwarranted, as it was general enough to be technology-agnostic.

PASC noted that a patient advocacy group was supportive of the application, particularly the impact on equity of access for treatment of disease with a high incidence and low survival rate.

Next steps

PASC noted that the applicants have elected to progress the application as an Applicant Developed Assessment Report (ADAR).

PASC noted that, should the application be successful, consequential changes would be required to the PBS restrictions for the ALK inhibitors and ROS1 inhibitors, which refer to the results of FISH testing as a criterion to determine a patient's eligibility for PBS subsidy (see Table 2). The simplest way to achieve this would be a streamlined codependent submission, such that the ADAR for MSAC is accompanied by a lower category submission to PBAC in relation to these PBS consequences.

Applicant Comments on the PICO Confirmation

Nil.

References

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