Australian Government

Department of Health

Ratified PICO Confirmation

Application 1669:

KRAS G12C variant testing in patients with non-squamous histology or histology not otherwise specified non-small cell lung cancer to help determine eligibility for PBS-subsidised sotorasib

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	**Test:** Patients with non-squamous (or histology not otherwise specified) non-small cell lung cancer (NSCLC). **Drug:** Patients with histologically or cytologically confirmed non-squamous or not otherwise specified (NOS) stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC, with WHO performance status 0-2, who have progressed on prior therapy, and whose tumour has the Kirsten rat sarcoma (*KRAS*) G12C variant.
Prior tests	Radiologic and pathologic investigation
Intervention	**Test:** *KRAS* G12C testing in patients with non-squamous (or histology not otherwise specified) NSCLC **Drug:** Sotorasib as a second-line therapy for patients found to be positive for *KRAS* G12C. Standard care in those negative for *KRAS* G12C.
Clinical utility standard	*Therascreen*® *KRAS* RGQ (Rotor-Gene Q) PCR kit (Qiagen) using DNA samples on formalin-fixed, paraffin embedded tumour tissue from a biopsy sample
Comparator	**Test:** No testing **Drug:** Docetaxel which is standard of care second-line therapy in patients without a currently actionable biomarker.
Outcomes	**Test outcomes:** Safety: adverse events associated with biopsy/re-biopsy Analytical performance of Australian test options compared to the clinical utility standard: • Positive percent agreement • Negative percent agreement Clinical validity of test: • Comparative prognosis of patients with advanced or metastatic NSCLC between those whose tumours do and do not have the *KRAS* G12C variant. Clinical utility of test: • Treatment effect modification of *KRAS* G12C in terms of response to sotorasib in patients with advanced or metastatic NSCLC. Other test-related considerations • Re-biopsy rates (including test failure and inadequate sample rate) • Test turn-around time **Drug outcomes:** • Safety and tolerability (adverse events [AEs], physical examinations, laboratory findings, vital signs) • Objective response rate • Overall survival • Progression-free survival • Partial response • Complete response • Health-related quality of life **Healthcare system:** • Cost of testing per patient with associated re-biopsies • Cost-effectiveness of testing and treatment • Financial implications

PICO or PPICO rationale for therapeutic and investigative medical services only

Research questions

What is the safety, effectiveness and cost-effectiveness of *KRAS* G12C variant testing to determine eligibility for PBS-subsidised sotorasib second-line therapy in patients with locally advanced or metastatic NSCLC, shown to have non-squamous histology or histology not otherwise specified?

Do results from *KRAS* G12C variant testing predict a treatment effect modification with sotorasib? Is this distinguishable from the variation in prognosis following the results of *KRAS* G12C variant testing?

How will the range of testing options likely to be used in Australian pathology practices compare (in regard to the extent of positive and negative discordance) to the clinical utility standard?

Is the proposed *KRAS* G12C variant testing safe in the test-eligible population compared with no testing?

Population

Test: The applicant proposed population for testing of *KRAS* G12C is "patients diagnosed with non-squamous histology or histology not otherwise specified (NOS) non-small cell lung cancer (NSCLC)", at the point of diagnosis, to determine their eligibility for PBS-subsidised second-line treatment with sotorasib of locally advanced or metastatic disease.

Drug: Patients with histologically or cytologically confirmed non-squamous or not otherwise specified (NOS) stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC, with WHO performance status 0-2, who have progressed on prior therapy, and whose tumour has the Kirsten rat sarcoma (*KRAS*) G12C variant.

Background

With more than 2 million new cases each year, lung cancer remains one of the most common cancers worldwide (Sung et al. 2021). In Australia, lung cancer was the 5th most commonly diagnosed cancer and estimated to remain 5th most commonly diagnosed in 2021 (AIHW 2021). It is estimated that there will be 13,810 cases of lung cancer diagnosed in 2021 in Australia increasing from 13,610 in 2020 (AIHW 2021). With the current age-standardised incidence rate of 42.6 per 100,000 people, the incidence rate of lung cancer is only expected to increase with age. Lung cancer is the leading cause of death among all the cancers in Australia with an estimated 26.5 deaths per 100,000 people in 2021 (AIHW 2021) and it is estimated that 8,693 people will die with lung cancer in Australia in 2021. The five-year survival data from 2013 to 2017 shows that only 20.2% of population diagnosed with lung cancer survived 5 years after diagnosis with a higher survival among females (24.7%) compared to males (17.0%) (AIHW 2021).

Lung cancers are classified into two main types; non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)[1]. NSCLC is the most common type accounting for about 86.6% of all lung cancers (Mitchell et al. 2013). NSCLC is further classified into three major sub-types:

- Adenocarcinoma – This cancer develops in mucus-producing cells and is commonly diagnosed in both smokers and non-smokers. This accounts for about 40% of all lung cancers.
- Squamous cell carcinoma – commonly develops in large airways of lungs.
- Large cell carcinoma - can appear in any part of the lung and are not clearly squamous cell or adenocarcinoma.

Approximately 30–40% of NSCLC patients present with metastatic disease at the time of diagnosis and about 30% of patients found to have locally advanced disease (Tamura et al. 2015) (Filippi et al. 2018).

Rationale for testing biomarker – KRAS G12C in NSCLC

Lung cancer represents one of the most mutated of solid tumours. Over the years, oncogenic drivers in NSCLC were identified and several targeted therapies have been developed to benefit the patients. Molecular genotyping has now become common and guiding the clinical care of patients with locally advanced or inoperable and metastatic lung adenocarcinomas.

Kirsten rat sarcoma (*KRAS*) oncogene is a G-protein with intrinsic GTPase activity and activating variants result in unregulated signalling through the MAP/ERK pathway (NCCN 2021). *KRAS* is the most frequently mutated oncogene in NSCLC. Variants in *KRAS* are most commonly seen at codon 12, although other variants can be seen in NSCLC. Whether the presence of the *KRAS* G12C variant is prognostic of poor survival is a matter for the assessment. Similar clinical management for patients with *G12C* and *non-G12C* variants in any stage lung adenocarcinoma result in poorer prognosis for patients with a *G12C* variant (SVATON et al. 2016) (Pan et al. 2016). About 30% (25% to 35%) of newly diagnosed NSCLC cases are found to have a *KRAS* variant out of which ~42% are identified to have a *G12C* variant (Arbour et al. 2021). Therefore, *KRAS* G12C variants can be identified in about 13% of newly diagnosed NSCLC cases. Owing to the low probability of overlapping targetable alterations, the presence of a *KRAS* G12C variant identifies patients who are unlikely to benefit from further molecular testing (Lindeman, Neal I. et al. 2018). It has also been found that *KRAS* pathogenic variants are early oncogenic events and do not alter over time, being preserved in the tumour (Kris et al. 2014) (Sherwood, J et al. 2015). Therefore, the applicant considered that there is no reason to delay testing of the *KRAS* G12C variant until the consideration of second-line therapy, which is when sotorasib is intended to be used.

The applicant also claimed that delaying *KRAS* G12C testing would result in attrition of tumour tissue, an increased rate of re-biopsy in NSCLC patients, and increased risk of biopsy-related morbidity. It therefore may be safer for NSCLC patients to perform *KRAS* G12C testing prior to the initiation of therapy at the same time as testing for *EGFR* pathogenic variants, under Medical Benefits Schedule (MBS) item 73337.

[1] https://www.cancercouncil.com.au/lung-cancer/

Utilisation of testing to detect KRAS G12C variant

There are two different methods for estimating the utilisation of the testing service. The epidemiology-based approach suggests that there will be 13,810 cases of lung cancer in 2021 in Australia, of which 86.6% (11,959 cases) will have NSCLC histology, and 74.2% of NSCLC tumours (8,874 cases) will have non-squamous/NOS histology. Thus, an estimated 8,874 patients would be eligible for *KRAS* G12C testing in Australia in 2021 (Table 1).

The market-based approach estimates the utilisation of the testing service based on previous utilisation of MBS item 73337. As the population for MBS item 73337 will remain the same, despite the proposed inclusion of *KRAS* G12C in addition to *EGFR* testing, the future uptake can be projected based on the previous utilisation of the MBS item 73337. This approach projects a utilisation of 5,135 services in Australia for 2021 (Table 2).

Given that i) not all patients would be willing to undergo testing, and ii) some patients would be tested within the public hospital system, and therefore not necessarily billed to the MBS, the market-based approach may be a more appropriate estimate of MBS service volumes than the epidemiology-based approach.

Table 1: Estimated uptake of *KRAS* G12C testing – epidemiology-based approach

Year	Incidence of lung cancer[a]	Estimated NSCLC cases[b]	Eligible for *KRAS* G12C testing[c]	*KRAS* G12C positive[d]
2015	11841	10254	7609	989
2016	12441	10774	7994	1039
2017	12585	10899	8087	1051
2018	12880	11154	8276	1076
2019	13218	11447	8494	1104
2020	13604	11781	8742	1136
2021	13810	11959	8874	1154
2022	14114	12222	9069	1179
2023	14406	12476	9257	1203
2024	14699	12729	9445	1228
2025	14991	12983	9633	1252
2026	15284	13236	9821	1277
2027	15577	13489	10009	1301

a – Estimates of incidence of lung cancer are based on the data available from AIHW for the years 2015 to 2021.

b – 86.6% of lung cancer cases are estimated to be NSCLC.

c – 74.2% of NSCLC are estimated to be non-squamous/NOS histology.

d - ~13% of tested population is found to be *KRAS* G12C positive.

The *KRAS* G12C variant is present in ~13% of NSCLC cases (Arbour et al. 2021), suggesting that approximately 667 patients might be eligible for the second-line treatment of locally advanced or metastatic disease with sotorasib in 2021. However, as testing is proposed to be conducted at diagnosis and followed by first-line treatment of locally advanced or metastatic disease, survival and frailty of the population after first-line therapy need to be taken into consideration while estimating the exact eligibility for sotorasib. It is anticipated that patients would be tested only once per lifetime, at initial diagnosis. The applicant considered that leakage to populations not targeted by the service

would be constrained by the MBS item descriptor to ensure testing is applied only where clinically indicated.

The number of people tested in the first two years may be slightly higher than the estimated numbers. This is because of the cases who previously underwent *EGFR* testing and were found to be negative may undergo *KRAS* G12C testing if the test is approved. However, it was noted in the pre-PASC meeting that the majority of those who have undergone *EGFR* testing will have had the test performed using a small gene panel, which already incorporates *KRAS* G12C variants. There is no restriction on the frequency of use of MBS item 73337, so if the item is amended to incorporate *KRAS* G12C testing, those patients who have not already been tested for *KRAS* G12C may claim the item again.

Table 2: Estimated uptake of *KRAS* G12C testing – market-based approach

	Year	Uptake[a]	*KRAS* G12C positive
Actuals from the MBS item report	2015	3368	438
	2016	3419	444
	2017	3863	502
	2018	4147	539
	2019	4603	598
	2020	4697	611
Projections	2021	5135	667
	2022	5464	710
	2023	5794	753
	2024	6123	796
	2025	6453	839
	2026	6783	882
	2027	7112	925

a – From year 2021, uptake is estimated based on the claims made for *EGFR* testing (MBS Item 73337) from 2015 to 2020.

Prior tests

The common diagnostic tests usually undertaken to detect lung cancer are chest x-ray, CT scan, PET scan, lung function test, biopsy, and sputum cytology. Prior testing procedures are common for both intervention and comparator.

Table 3 summarises the prior investigative procedures to detect non-squamous or NOS histology NSCLC.

Other tests which occur at the point of diagnosis (for both the intervention and comparator scenario), are *EGFR* testing, and immunohistochemistry (IHC) testing of PD-L1, and for triage testing of ALK and ROS1.

Table 3: Investigative procedures to detect lung cancer

	Mandatory	Optional
General	Medical history Physical examination Assessing comorbidity PS	
Imaging	X-ray thorax CT thorax PET-CT thorax MRI brain	Bone scintigraphy Contrast enhanced CT-brain
Laboratory	Blood cell counts Renal function Liver enzymes Bone parameters	
Cardio-pulmonary function	FVC, FEV1, DLCO, ECG If indicated: CPET	Ejection fraction CAG
Tissue Procurement	Bronchoscopy EBUS/EUS mediastinal nodes CT-guided biopsy	Mediastinoscopy

Source: (Postmus et al. 2017)

CAG = coronary angiography; CPET = cardio pulmonary exercise testing; CT = computed tomography; DLCO = diffusing capacity of the lungs for carbon monoxide; EBUS = endoscopic bronchial ultrasound; ECG = electrocardiogram; EUS = endoscopic ultrasound; FEV1 = forced expiratory volume in 1 second; FVC = forced expiratory vital capacity; MRI = magnetic resonance imaging; PET-CT = positron emission tomography computed tomography; PS = performance status

Intervention

Test:

Purpose of the test:

The proposed test is *KRAS* G12C testing in patients diagnosed with non-squamous histology or histology NOS NSCLC. The applicant proposes to include *KRAS* G12C testing in the existing MBS item 73337 (see Table 5 on page 18 for more details).

The purpose of the proposed test is to determine the eligibility for PBS-subsidised sotorasib second-line therapy in patients with locally advanced or metastatic NSCLC, shown to have non-squamous histology/histology NOS.

Methods of testing:

The proposed test is an *in vitro* diagnostic test and does not specify any particular technology or platform. Any accredited and validated testing of *KRAS* G12C is within the scope of the application. The options currently available are:

- Single genes using direct or Sanger sequencing,
- Single genes using polymerase chain reaction (PCR)-based methods (e.g. the *Therascreen®* *KRAS* RGQ PCR kit),
- Multiple genes using matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (MS),
- Multiple genes using targeted next generation sequencing (NGS) with a small gene panel, and

- Comprehensive genomic profiling using very large NGS panels.

Most of the molecular pathology testing services in Australia currently use small gene panels on NGS platforms. These laboratories are already testing for *KRAS* pathogenic variants due to its inclusion in NSCLC gene panels along with *EGFR*. There are a few laboratories using single-gene testing by PCR-based methods. In the event that the parallel application for comprehensive genomic profiling for patients with NSCLC (MSAC application 1634) receives funding approval, the applicant has no objection to KRAS testing being incorporated into this proposed MBS item.

PASC noted that most testing of KRAS *in Australia is done using next-generation sequencing with gene panels that include* KRAS*. PASC mentioned that some smaller laboratories may still be using single gene testing. However, the applicant claimed that none of the laboratories included in a small survey, and none of the hospital centres included in a large survey, reported conducting single gene testing of* KRAS G12C*.*

The initial steps in both NGS and PCR methods include:

- extraction,
- isolation, and
- quantification of tumour DNA from the biopsy specimens.

The DNA is extracted from formalin fixed paraffin embedded (FFPE) tumour biopsy samples.

PASC noted that the test was proposed to be pathologist determinable like testing for EGFR*. PASC advised that cytology samples should be eligible if confirmed by a pathologist to have adequate tumour tissue fragments for assessment.*

Next steps involved in NGS methods include:

- preparation of sequencing libraries,
- enrichment of sequencing libraries for the genes of interest,
- sequencing of enriched libraries, and
- analysis and reporting of test results.

Next steps involved in PCR-based methods:

- amplification,
- post-PCR analysis, and
- reporting of test results.

Studies have shown that PCR-based methods demonstrated concordance with NGS methods in NSCLC (Sherwood, JL et al. 2017). However, NGS methods detected rare *EGFR* and *KRAS* pathogenic variants which will not be detected by PCR assays which only detect the specific variants for which primers are included.

Registration status of testing devices:
The *in vitro* diagnostic devices used for the proposed testing are classified as Class III under Therapeutic Goods Administration (TGA). The applicant has identified many manufacturers supplying these devices which are registered in the Australian Register of Therapeutic Goods (ARTG) by the TGA. Some of the most commonly used registered devices include:

Thermo Fisher Scientific Australia Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 256113
Product name: Acquired genetic alteration IVDs
Sponsor: Thermo Fisher Scientific Australia Pty Ltd
Manufacturer: Microgenics Corporation

Illumina Australia Pty Ltd – Human genetics-related IVDs
ARTG ID: 297844
Product name: Human genetics related IVDs
Sponsor: Illumina Australia Pty Ltd
Manufacturer: Illumina Inc

Clinical utility standard:
The *Therascreen® KRAS* RGQ (Rotor-Gene Q) PCR Kit manufactured by Qiagen is the clinical utility standard (used in the key trial demonstrating the clinical utility of *KRAS* G12C testing and treatment with sotorasib). The *Therascreen®* kit uses DNA extracted from formalin-fixed paraffin embedded (FFPE) tumour biopsy samples. However, the *Therascreen®* kit is not yet registered as a companion diagnostic test for sotorasib in NSCLC. The applicant confirmed that a regulatory application for the *Therascreen® KRAS* RGQ (Rotor-Gene Q) PCR Kit was submitted to the TGA in May 2021 as a companion diagnostic test to aid clinicians in the identification of NSCLC cancer patients who may be eligible for treatment with sotorasib, based on a positive *KRAS* G12C pathogenic variant result. *However, PASC confirmed that, although Therascreen® is the clinical utility standard, other test options are available to be used in Australia.*

Health professionals:
The request for the proposed testing would come from patient's treating clinician prior to the initiation of therapy. Medical oncologists and thoracic physicians are the most likely specialists or consultant physicians requesting for the test. However, as testing is proposed to be conducted at diagnosis along with *EGFR* testing, *KRAS* testing should also be pathologist determinable (since the biopsy is usually submitted to make a diagnosis of malignancy).

Both PCR-based and NGS assays would be conducted by pathologists and laboratory technicians (Approved Pathology Practitioners in Accredited Pathology Laboratories as defined in the MBS Pathology table), with results of testing being reported back to the treating clinician to guide treatment selection.

Frequency of test:
Most of the NSCLC patients would require only one *KRAS* G12C testing in their lifetime because *KRAS* pathogenic variants are known to be stable over time. However, re-testing may be required in a small group of patients if initial DNA testing is inconclusive. In another small group of patients, re-biopsy might be required if there is inadequate tissue remaining for *KRAS* G12C testing (with associated costs and clinical risks).

Drug:
The proposed testing is to help determine eligibility for second-line therapy with sotorasib in patients diagnosed with advanced or metastatic non-squamous/NOS histology NSCLC and identified to be positive for *KRAS* G12C variant. Therefore, the intervention drug is sotorasib in those found to be positive for *KRAS* G12C and standard of care (docetaxel) in those found to be negative.

Sotorasib specifically and irreversibly inhibits *KRAS* G12C by trapping it in the inactive GDP-bound state (Hong et al. 2020). Phase 1 trials of sotorasib were conducted in patients with advanced solid tumours identified to have a *KRAS* G12C variant. Phase 1 trials showed promising anticancer activity among patients with heavily pre-treated advanced solid tumours (Hong et al. 2020). About 11% of patients were found to have grade 3 or 4 treatment-related adverse effects.

The applicant claimed that use of *KRAS* G12C testing and access to sotorasib will not change the use of first-line treatments for locally advanced or metastatic non-squamous or NOS NSCLC in patients without *EGFR* variants (immunotherapy ± chemotherapy).

Registration status of the drug:
The applicant confirmed that the registration application of sotorasib has been accepted for evaluation under the TGA's provisional pathway process. Initial provisional registration will be based on the phase 2 component of a phase1/2 trial (NCT03600883) with conversion to full registration once the phase 3 trial (NCT04303780) is completed. Sotorasib has also received TGA orphan designation.

Comparator

The proposed comparator reflects the current testing and treatment pathways for patients with NSCLC shown to have non-squamous/NOS histology.

Test:
In the current treatment pathway for patients with NSCLC, there is no *KRAS* G12C testing. The comparator therefore is 'no *KRAS* testing'. The proposed medical testing is expected to be an add-on test.

Drug:
The applicant proposes Docetaxel as the standard second-line treatment in patients with no actionable biomarkers in advanced or metastatic non-squamous/NOS histology NSCLC. No objection regarding the use of docetaxel as the main comparator has been raised by the PBAC Secretariat in pre-submission meetings with the applicant.

Alternative second-line treatments for advanced or metastatic non-squamous/NOS histology NSCLC available in Australia include pemetrexed, nivolumab and atezolizumab. The applicant advised that 1st-line treatment predominantly consists of PD-(L)1 inhibitors, usually in combination with chemotherapy. In the minority of patients unsuitable for PD-(L)1 inhibitors, 1st-line treatment would be platinum doublet chemotherapy. In both instances, the chemotherapy will include pemetrexed (so it would not be used 2nd line). Use of PD-(L)1 inhibitors on the PBS is limited to "once-per-lifetime". Therefore, use of nivolumab and atezolizumab would also be uncommon at 2nd-line.

Outcomes

Test-related outcomes:
Safety:
Adverse events associated with biopsy/re-biopsy for patients with inadequate tissue for tumour testing.

Analytical performance of Australian test options compared to the clinical utility standard:

- Positive percentage agreement
- Negative percentage agreement

Clinical validity of the test:

Evaluate the comparative prognosis of patients with advanced or metastatic NSCLC between those whose tumours do and do not have the KRAS G12C variant.

Clinical utility of the test:

Determine whether testing for *KRAS* G12C predicts variation in the treatment effect of sotorasib in terms of health outcomes for patients.

Other test-related considerations:

- Re-biopsy rates (also include test failure and inadequate sample rate as a proxy for re-biopsy rate)
- Test turn-around time.

Drug-related outcomes:

Safety outcomes:

Safety and tolerability of treatment with sotorasib or docetaxel (adverse events, physical examinations, laboratory findings and vital signs).

Clinical effectiveness outcomes:

- Objective response rate
- Overall survival
- Progression-free survival
- Partial response
- Complete response
- Health-related quality of life

Healthcare system:

- Cost of testing per patient with associated re-biopsies
- Cost-effectiveness of testing and treatment
- Financial implications

Clinical management algorithms

Current clinical management algorithm for identified population

In current clinical management, the identified population does not undergo any testing for *KRAS* G12C and there is no targeted therapy for those patients harbouring the *KRAS* G12C variant. After being diagnosed with non-squamous/NOS histology NSCLC, patients undergo *EGFR* testing and IHC testing for PD-L1, ALK and ROS1 triaging. Those found to be *EGFR* wildtype further undergo *ALK* and/or *ROS1* FISH testing at the point of being locally advanced or metastatic, depending on ALK and ROS1 triage status. Those identified to be positive for any of the relevant pathogenic variants undergo treatment with targeted therapies. Those found to have no actionable biomarkers are treated with immunotherapy ± chemotherapy as first-line therapy. If progressed they receive a second-line

therapy. Docetaxel is the nominated second-line therapy for those identified to have no actionable biomarkers for this application.

The current population of interest for the proposed second-line treatment with sotorasib are those found to have no actionable biomarkers and so are treated with immunotherapy ± chemotherapy as first-line therapy. Such patients, who may be harbouring the *KRAS* G12C variant, are identified in green in the clinical algorithm below (Figure 1). The current clinical algorithm was based on the current clinical algorithm from the ratified PICO 1634 – comprehensive genomic profiling of non-squamous NSCLC using next generation sequencing.

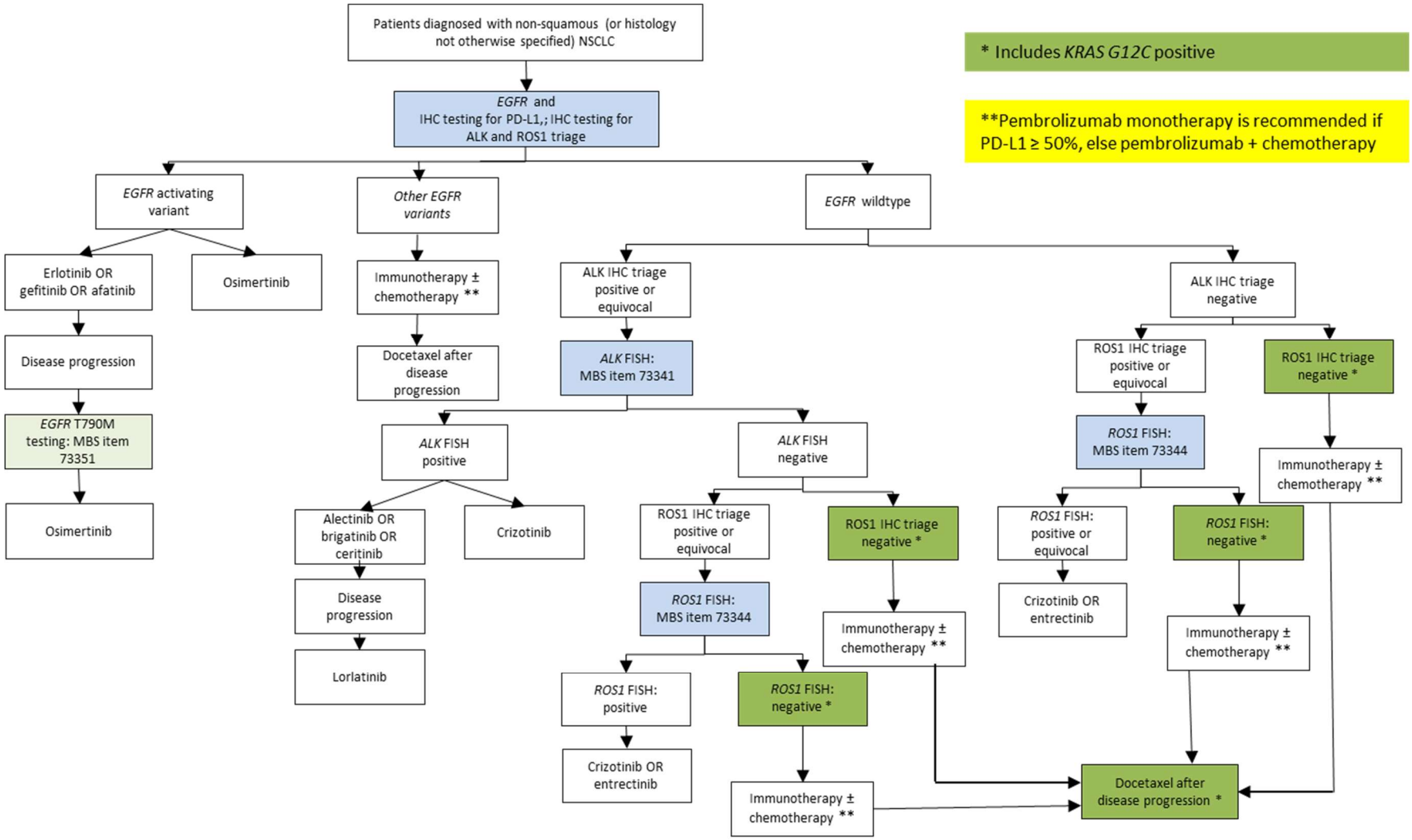

Figure 1 Current clinical algorithm (without *KRAS* G12C testing)

Proposed clinical management algorithm for identified population

The proposed clinical management algorithm (Figure 2) introduces *KRAS* G12C testing at the point of diagnosis along with *EGFR* testing and IHC testing of PD-L1, and ALK and ROS1 triaging. Further testing and treatment management would depend on the status of *EGFR* and *KRAS* variants. There would be no change in the clinical management of those identified to have an activating *EGFR* variant.

Owing to the mutual exclusivity of the variants being tested, it is proposed that the addition of *KRAS* testing would replace confirmatory *ALK* and *ROS1* FISH testing in those with a *KRAS* G12C variant or any other pathogenic *KRAS* variants. First-line therapy in this groups would remain the same, which is immunotherapy ± chemotherapy. However, sotorasib would be considered for second-line therapy in those with *KRAS* G12C variants after the disease progression.

Second-line treatment for those without *KRAS* G12C variants would be standard care (docetaxel).

PASC advised that, if this application were successful, the item descriptors for ALK and ROS1 FISH testing (73341 and 73344, respectively) would need to be modified to add "with documented absence of KRAS *pathogenic variants".*

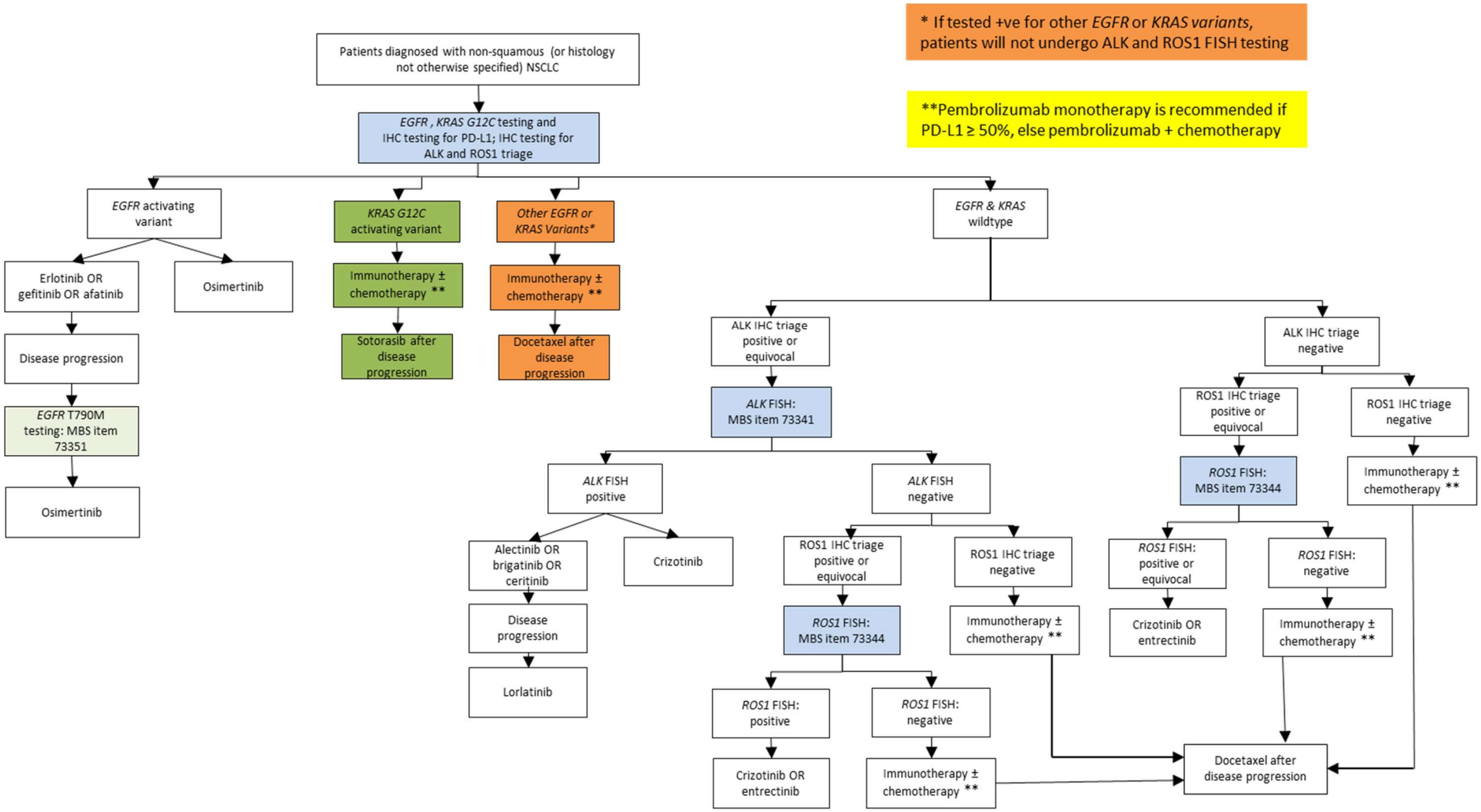

Figure 2 Proposed clinical algorithm for NSCLC at time of diagnosis (with *KRAS* G12C testing)

Proposed economic evaluation

The applicant proposed that the overall clinical claim for the proposed medical service (*KRAS* G12C testing and treatment with sotorasib) is superior in regard to both safety and effectiveness compared to the main comparator (no *KRAS* G12C testing and docetaxel) in patients with NSCLC. Given the claim of clinical superiority, the appropriate type of economic evaluation is a cost-effectiveness or cost-utility analysis.

Table 4: 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

PASC noted that applicant indicated a claim of superior safety for sotorasib.

Proposed item descriptor

The applicant proposed an amendment to the existing MBS item 73337. The existing MBS item 73337 is for the *EGFR* testing in patients diagnosed with non-squamous/NOS histology to determine the access to PBS-subsidised TKI inhibitors. The addition of *KRAS* G12C testing in the same population would be to determine access to sotorasib; a second-line drug for the treatment of advanced or metastatic non-squamous/NOS histology NSCLC.

PASC noted that the proposal was for KRAS *testing to be added to the existing* EGFR *testing MBS item, allowing testing of* EGFR *or* KRAS*.*

The purpose of allowing the item to be still used to test a single gene was to cover the transition period, where some patients have already tested negative for EGFR *variants, but have not yet been tested for* KRAS*. However, PASC was concerned that this would also create a longer-term incentive for laboratories to charge twice when both* EGFR *and* KRAS *were tested. PASC suggested that further advice would need to be provided by the Department of Health in regard to the wording of the item descriptor to avoid any double billing. PASC also considered that laboratories performing PCR-based testing would be at a disadvantage if the wording was modified to require testing of both* EGFR *and* KRAS *in all cases. However, PASC acknowledged that all laboratories will be shifting to panel testing in*

near future, especially as this would optimise the multiple testing of a typically small tissue sample. PASC concluded that the wording should reflect the main intent of reducing the risk of double billing.

Table 5: Proposed amended MBS item 73337

Category 6 – PATHOLOGY SERVICES
MBS Item: 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: 1. 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; or 2. the requirements relating to Kirsten rat sarcoma oncogene (*KRAS*) G12C variant status for access to sotorasib under the Pharmaceutical Benefits Scheme are fulfilled. Fee: $397.35 (unless an alternative cost can be supported)

NB: Proposed amendments to MBS 73337 are highlighted

Proposed fee

The applicant proposed that there would not be any change in the cost of MBS item 73337 due to the addition of *KRAS* G12C testing as most pathology laboratories in Australia already include *KRAS* testing in their testing panels. The proposed fee is therefore $397.35. However, the ADAR may need to consider the impact of the inclusion of *KRAS* G12C testing on laboratories which are still using a single-gene PCR-based method. At the pre-PASC meeting, the applicant advised it would contact the Royal College of Pathologists (RCPA) regarding the proposed fee.

The cost of genetic testing varies based on the number of genes tested and the method used (NGS or PCR based). A review of the MBS item 73337 suggests the average fee charged was $489 in 2015-16 and varied across the states.

Table 6: Fees charged for MBS item 73337 for 2015-16

	NSW	VIC	QLD	SA	WA	Australia
Average fee charged	$483	$448	$504	$457	$546	$489
Median fee	$514	$397	$517	$397	$556	$514
Bulk billing rate	80%	79%	38%	49%	25%	69%

Source:https://www1.health.gov.au/internet/msac/publishing.nsf/Content/06A73A3B56D88650CA25801000123B8C/$File/1161%20and%201173%20PSD.pdf

PASC acknowledged that the average and median fees for EGFR *testing reported in 2015-16 were well over the MBS fee of $397.35, although PASC also noted that this may have reduced subsequently over the last five years. PASC noted that the applicant assumed that the testing would be cost-neutral, and expressed concerned about this assumption. The applicant stated that it was awaiting further input from the Royal College of Pathologists of Australasia regarding whether* KRAS *testing can be absorbed into the costs of* EGFR *testing.*

Summary of public consultation input

The Department received targeted consultation feedback from:

- The Lung Foundation Australia (LFA); and

- The National Pathology Accreditation Advisory Council (NPAAC).

The LFA was supportive of the application, stating that early identification of genomic variants would facilitate timely access to targeted therapies, improving quality of life and treatment outcomes to lung cancer patients. The LFA also noted that this application would allow for equitable access to testing, thus improving access to treatment and improving health outcomes. However, the LFA did observe that tissue samples may not be adequate and may require re-biopsy, that follow -up testing should be available due to disease progression and, that the application is limited to the use of solid tissue.

NPAAC considered that there were no implementation issues regarding *KRAS* testing, as it is a highly reproducible test with an existing external quality assurance program (QAP).

PASC discussed that the current QAP for KRAS *testing was for colon cancer, not lung cancer, but that a QAP in lung cancer would be easy to implement. There is currently the option of participation in an EMQN program for* KRAS *testing in lung cancer.*

Next steps

The applicant advised that it would be lodging an Applicant Developed Assessment Report.

Applicant Comments on the PICO Confirmation

Population

The applicant advised as a point of clarification, that sotorasib use would not be strictly limited to second-line. The proposed PBS listing will include the wording: "The condition must have progressed on or after prior therapy for this condition". However, it is recognised that use of sotorasib will predominantly be in the second-line setting.

References

AIHW 2021, *Cancer data in Australia*, AIHW, Canberra, <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia>.

Arbour, KC, Rizvi, H, Plodkowski, AJ, Hellmann, MD, Knezevic, A, Heller, G, Yu, HA, Ladanyi, M, Kris, MG, Arcila, ME, Rudin, CM, Lito, P & Riely, GJ 2021, 'Treatment Outcomes and Clinical Characteristics of Patients with *KRAS*-G12C–Mutant Non–Small Cell Lung Cancer', *Clinical Cancer Research*, vol. 27, no. 8, pp. 2209-2215.

Filippi, AR, Di Muzio, J, Badellino, S, Mantovani, C & Ricardi, U 2018, 'Locally-advanced non-small cell lung cancer: shall immunotherapy be a new chance?', *Journal of thoracic disease*, vol. 10, no. Suppl 13, pp. S1461-S1467.

Hong, DS, Fakih, MG, Strickler, JH, Desai, J, Durm, GA, Shapiro, GI, Falchook, GS, Price, TJ, Sacher, A, Denlinger, CS, Bang, YJ, Dy, GK, Krauss, JC, Kuboki, Y, Kuo, JC, Coveler, AL, Park, K, Kim, TW, Barlesi, F, Munster, PN, Ramalingam, SS, Burns, TF, Meric-Bernstam, F, Henary, H, Ngang, J, Ngarmchamnanrith, G, Kim, J, Houk, BE, Canon, J, Lipford, JR, Friberg, G, Lito, P, Govindan, R & Li, BT 2020, '*KRAS*(G12C) Inhibition with Sotorasib in Advanced Solid Tumors', *N Engl J Med*, vol. 383, no. 13, Sep 24, pp. 1207-1217.

Kris, MG, Johnson, BE, Berry, LD, Kwiatkowski, DJ, Iafrate, AJ, Wistuba, II, Varella-Garcia, M, Franklin, WA, Aronson, SL, Su, P-F, Shyr, Y, Camidge, DR, Sequist, LV, Glisson, BS, Khuri, FR, Garon, EB, Pao, W, Rudin, C, Schiller, J, Haura, EB, Socinski, M, Shirai, K, Chen, H, Giaccone, G, Ladanyi, M, Kugler, K, Minna, JD & Bunn, PA 2014, 'Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs', *JAMA*, vol. 311, no. 19, pp. 1998-2006.

Lindeman, NI, Cagle, PT, Aisner, DL, Arcila, ME, Beasley, MB, Bernicker, EH, Colasacco, C, Dacic, S, Hirsch, FR, Kerr, K, Kwiatkowski, DJ, Ladanyi, M, Nowak, JA, Sholl, L, Temple-Smolkin, R, Solomon, B, Souter, LH, Thunnissen, E, Tsao, MS, Ventura, CB, Wynes, MW & Yatabe, Y 2018, 'Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology', *Arch Pathol Lab Med*, vol. 142, no. 3, Mar, pp. 321-346.

Lindeman, NI, Cagle, PT, Aisner, DL, Arcila, ME, Beasley, MB, Bernicker, EH, Colasacco, C, Dacic, S, Hirsch, FR, Kerr, K, Kwiatkowski, DJ, Ladanyi, M, Nowak, JA, Sholl, L, Temple-Smolkin, R, Solomon, B, Souter, LH, Thunnissen, E, Tsao, MS, Ventura, CB, Wynes, MW & Yatabe, Y 2018, 'Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology', *Journal of Thoracic Oncology*, vol. 13, no. 3, 2018/03/01/, pp. 323-358.

Mitchell, PL, Thursfield, VJ, Ball, DL, Richardson, GE, Irving, LB, Torn-Broers, Y, Giles, GG & Wright, GM 2013, 'Lung cancer in Victoria: are we making progress?', *Med J Aust*, vol. 199, no. 10, Nov 18, pp. 674-679.

NCCN 2021, 'NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Non-Small Cell Lung Cancer (Version 5.2021)'.

Pan, W, Yang, Y, Zhu, H, Zhang, Y, Zhou, R & Sun, X 2016, '*KRAS* mutation is a weak, but valid predictor for poor prognosis and treatment outcomes in NSCLC: A meta-analysis of 41 studies', *Oncotarget*, vol. 7, no. 7, pp. 8373-8388.

Postmus, PE, Kerr, KM, Oudkerk, M, Senan, S, Waller, DA, Vansteenkiste, J, Escriu, C & Peters, S 2017, 'Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†', *Annals of Oncology*, vol. 28, 2017/07/01/, pp. iv1-iv21.

Sherwood, J, Dearden, S, Ratcliffe, M & Walker, J 2015, 'Mutation status concordance between primary lesions and metastatic sites of advanced non-small-cell lung cancer and the impact of mutation testing methodologies: a literature review', *Journal of Experimental & Clinical Cancer Research*, vol. 34, no. 1, 2015/09/04, p. 92.

Sherwood, JL, Brown, H, Rettino, A, Schreieck, A, Clark, G, Claes, B, Agrawal, B, Chaston, R, Kong, BSG, Choppa, P, Nygren, AOH, Deras, IL & Kohlmann, A 2017, 'Key differences between 13 *KRAS* mutation detection technologies and their relevance for clinical practice', *ESMO open*, vol. 2, no. 4, pp. e000235-e000235.

Sung, H, Ferlay, J, Siegel, RL, Laversanne, M, Soerjomataram, I, Jemal, A & Bray, F 2021, 'Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries', *CA: A Cancer Journal for Clinicians*, vol. 71, no. 3, pp. 209-249.

SVATON, M, FIALA, O, PESEK, M, BORTLICEK, Z, MINARIK, M, BENESOVA, L & TOPOLCAN, O 2016, 'The Prognostic Role of *KRAS* Mutation in Patients with Advanced NSCLC Treated with Second- or Third-line Chemotherapy', *Anticancer Research*, vol. 36, no. 3, pp. 1077-1082.

Tamura, T, Kurishima, K, Nakazawa, K, Kagohashi, K, Ishikawa, H, Satoh, H & Hizawa, N 2015, 'Specific organ metastases and survival in metastatic non-small-cell lung cancer', *Molecular and clinical oncology*, vol. 3, no. 1, pp. 217-221.