



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1669 – KRAS G12C variant testing to determine eligibility for PBS-subsidised sotorasib second-line therapy in patients with locally advanced or metastatic non small cell lung cancer

Applicant: Amgen Australia Pty. Ltd.

Date of MSAC consideration: 31 March – 1 April 2022

1. Purpose of application

The integrated codependent application was received from Amgen Australia Pty. Ltd. by the Department of Health, and requested:

- Medicare Benefits Schedule (MBS) listing of a test for the identification of the Kirsten rat sarcoma viral oncogene homologue (*KRAS*) G12C variant to determine eligibility for treatment with sotorasib in patients diagnosed with advanced (stage IIIB/IV) non-squamous or not otherwise specified (NOS) non-small cell lung cancer (NSCLC)
- Pharmaceutical Benefits Scheme (PBS) Section 85 Authority Required listing of sotorasib for the treatment of advanced (stage IIIB/IV) non-squamous or NOS NSCLC in patients who have evidence of the *KRAS* G12C variant.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC deferred its decision regarding testing for *KRAS* G12C variants in tumour tissue from patients with NSCLC, shown to have non-squamous histology or histology not otherwise specified. MSAC foreshadowed that it would expeditiously reconsider this testing if the Pharmaceutical Benefits Advisory Committee (PBAC) recommends sotorasib for those eligible patients in this population in whom a *KRAS* G12C variant is detected.

Consumer summary

This application was from Amgen Australia Pty. Ltd. The part of the application considered by MSAC was to list genetic testing to detect the Kirsten rat sarcoma viral oncogene homologue (*KRAS*) G12C variant on the Medicare Benefits Schedule (MBS) for

Consumer summary

patients with certain types of advanced lung cancer. This *KRAS* G12C variant is quite common in lung cancer, but despite being a recognised oncogenic driver (i.e. a genetic change that is likely to make a cancer develop and then worsen), no effective therapy targeting this variant has previously been made. If the test result is positive, the person could be eligible to receive a medicine called sotorasib on the Pharmaceutical Benefits Scheme (PBS). Sotorasib was made to specifically target the *KRAS* G12C variant in people with advanced lung cancer.

The applicant proposed that *KRAS* G12C genetic testing be added to an existing MBS item (73337) which funds testing of the epidermal growth factor receptor (*EGFR*) gene. Many laboratories are already testing for *KRAS* G12C status when they are testing a tumour for *EGFR* gene status. This testing is frequently done as part of a genetic panel, which means that several genes are tested at once. MSAC therefore considered it was reasonable to include *KRAS* G12C testing in the item descriptor without increasing the fee.

MSAC considered that testing people with this type of advanced lung cancer would accurately identify the *KRAS* G12C variant and thus help determine eligibility for sotorasib. MSAC will quickly reconsider this application if the Pharmaceutical Benefits Advisory Committee (PBAC) recommends listing sotorasib as requested.

MSAC's advice to the Commonwealth Minister for Health

MSAC considered testing for *KRAS* G12C status to be safe, effective and cost-effective, but deferred its decision about listing it on the MBS. MSAC noted it would quickly reconsider this application if the PBAC recommends listing sotorasib on the PBS.

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

MSAC noted that this was an integrated codependent application from Amgen Australia Pty. Ltd. to include genetic testing for the *KRAS* G12C variant into the existing MBS item 73337 for epidermal growth factor receptor (*EGFR*) testing in patients with non-squamous or NOS NSCLC, to determine eligibility for treatment with sotorasib for the treatment of advanced (stage IIIB/IV) NSCLC.

MSAC noted that the March 2022 PBAC meeting decided to not recommend listing sotorasib on the PBS for the treatment of patients with non-squamous or NOS Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC who harbour the *KRAS* G12C variant and who have progressed on prior therapy.

MSAC noted that *KRAS* G12C variant testing is proposed to occur concurrently with pathogenic *EGFR* variant testing at initial diagnosis of non-squamous or NOS NSCLC. MSAC considered this timing of testing to be suitable because *KRAS* pathogenic variants are known to be stable over time. MSAC accepted advice that, in the majority of pathology laboratories in Australia, genetic testing using polymerase chain reaction (PCR) panels or next generation sequencing (NGS) would be used to analyse the presence of pathogenic variants in both *EGFR* and *KRAS*. MSAC noted that, currently, the turnaround time for reporting the results of PCR panels is usually several hours, whilst the turnaround time for reporting the results of NGS is usually several days. MSAC considered that the PCR and

NGS technologies were both mature in testing NSCLC tumours because testing for *KRAS* pathogenic variants is already included in NSCLC gene panels along with *EGFR* testing. National Association of Testing Authorities, Australia has accredited the proposed gene panels, and an external quality assurance program (QAP) is available.

MSAC noted no proposed change in the existing fee for MBS item 73337, as the current fee covers the cost of NGS panel testing (\$397.35). MSAC noted the consultation feedback received did not agree with the proposed fee, citing the extra costs associated with reporting *KRAS* results, validating *KRAS* testing in NSCLC specimens and ongoing participation in additional QAPs are not covered by the current *EGFR* MBS item 73337 and fee. On balance, MSAC considered it was reasonable to include *KRAS* G12C testing in the item descriptor without increasing the fee. MSAC noted that Application 1634 – *Comprehensive genomic profiling of non-small cell lung cancer tumour tissue specimens using next generation sequencing assays*, was considered by PASC in April 2021 and proposes a comprehensive gene panel test for NSCLC biomarkers.

MSAC also noted that the consultation feedback stating that it was unclear whether a laboratory using multigene assays or NGS would make a single claim for both *EGFR* and *KRAS*, or whether laboratories performing single gene tests would claim *EGFR* and *KRAS* separately and suggesting an alteration to the *ALK* and *ROS1* item descriptors to state that both *EGFR* and *KRAS* should be negative prior to proceeding with testing these genes. MSAC advised that MBS item 73337 should be restricted to “once per tumour diagnosis” if *KRAS* testing was included.

MSAC noted that item 73337 is pathologist determinable. MSAC supported continuation of this arrangement, but noted that the Department will consult further with the Royal College of Pathologists of Australasia (RCPA) to confirm what appropriate restrictions should be in place for a pathologist to determine that the test is necessary in the absence of a request from a treating practitioner.

MSAC accepted that adding *KRAS* testing to *EGFR* testing alone in MBS item 73337 would not change the safety profile of the overall test. Although a rebiopsy may be necessary if insufficient DNA is obtained through the original biopsy sample, MSAC considered that this was rare and would not increase with the addition of *KRAS* testing.

MSAC noted the prognostic evidence was informed from 13 studies of which the majority were of good quality. MSAC agreed with the ESCs and considered that most studies assessing the prognostic value of *KRAS* G12C compared with *KRAS* wild type or other *KRAS* variants were of low risk of bias and showed no significant differences in progression-free or overall survival.

MSAC considered that the rationale for codependency was based on biological plausibility. As such, predictive value was assumed as the Codebreak 100 study only enrolled patients with NSCLC who were *KRAS* G12C positive. MSAC considered this was acceptable as sotorasib is a first in class medicine targeting the *KRAS* G12C variant, and thus designing a trial that treated people without the pathogenic variant would have been difficult to justify ethically.

MSAC accepted there was high concordance between NGS (the most commonly used technique in Australia) and the clinical utility standard test used in the Codebreak 100 study (*therascreen KRAS* PCR kit) for detecting pathogenic *KRAS* variants, but noted the evidence

was limited to a single study with small patient numbers (see Table 5). MSAC also noted that the research-based limit of detection study by Sherwood et al. (2017) found that both the PCR kits and several NGS methodologies performed well with limits of detection at or below 10%, and considered that the main issue leading to variation in results relates to the quality of the tumour sample.

MSAC noted that 8 studies were assessed reporting the prevalence of any pathogenic *KRAS* variant as being 37.5% (range 24–49) and the prevalence of the *KRAS* G12C variant as being 14.5% (range 10–20).

MSAC noted that the base case structure of the modelled economic evaluation of sotorasib did not incorporate a testing component as it assumed perfect test performance (i.e. 100% sensitivity and specificity) based on the high concordance of PCR and NGS, and that testing is associated with no additional cost based on the claim that *KRAS* variant testing would occur with all current *EGFR* variant testing using NGS. MSAC noted that it is well-known that NGS performed with poor quality or inadequate tumour DNA samples has an increased likelihood of having a false negative result, but accepted that sensitivity analyses demonstrated that the incremental cost-effectiveness ratio (ICER) was insensitive to variation in test performance parameters (see Table 6).

MSAC noted that the submission claimed no change in the volume of testing related to MBS item 73337, and thus no additional cost to the MBS. MSAC also noted the pre-subcommittee response acknowledged that there may be a small increase in MBS testing costs from a small number of low throughput laboratories still using single-gene testing, but the applicant did not anticipate a large volume of catch-up testing would be required. Overall, MSAC accepted the cost-neutrality of adding *KRAS* G12C testing to MBS item 73337.

Overall, MSAC considered that testing for *KRAS* G12C status is safe, effective and cost-effective, but deferred its decision about listing it on the MBS. MSAC foreshadowed that it would expeditiously reconsider this testing if PBAC recommends sotorasib for those eligible patients in this population in whom a *KRAS* G12C variant is detected.

4. Background

MSAC has not previously considered *KRAS* G12C testing for access to sotorasib for the treatment of advanced stage IIIB/IV NSCLC.

MBS item 73337

At the 25-26 November 2021 meeting for application 1642, MSAC supported the replacement of “pembrolizumab” by “an immunotherapy listed” in the item descriptor for MBS item 73337. See App No. 1642 Public Summary Document [PSD] 2021, p3, and Table 2 below.

5. Prerequisites to implementation of any funding advice

In May 2021, Qiagen Australia submitted an application to the Therapeutic Goods Administration (TGA) for the registration of the companion diagnostic *therascreen KRAS* PCR Kit to identify the *KRAS* G12C variant so that it could be targeted by sotorasib.

Other PCR-based assays available for *KRAS* pathogenic variant testing in Australia include the Idylla™ *KRAS* Mutation Test (Biocartis) and the cobas® *KRAS* Mutation Test (Roche Diagnostics).

The NGS platforms that are most frequently used in Australia are manufactured by Illumina and ThermoFisher. They are most often used with a standard targeted gene panel which includes the *KRAS* gene, such as the TruSight Oncology panels from Illumina and the Ion AmpliSeq Cancer panels from ThermoFisher Scientific. These are designed to detect pathogenic variants in multiple genes at the same time. Laboratories using these panels as the basis for their “in-house” tests, are individually required to perform the necessary validations, gain the National Association of Testing Authorities (NATA) accreditation, and notify the TGA.

6. Proposal for public funding

The MBS listing proposed by the submission is a modified version of MBS item 73337 which is consistent with the MBS item agreed in the ratified PICO Confirmation (Table 1). The potential for double claiming based on the restriction as written was identified as an issue at the PASC meeting.

Table 1 Proposed MBS listing

Category 6 – PATHOLOGY SERVICES
<p>73337</p> <p>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:</p> <ol style="list-style-type: none"> 1. the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to erlotinib, gefitinib or afatinib under the Pharmaceutical Benefits Scheme 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. <p>Fee: \$397.35 Benefit: 75% = \$298.05 85% = \$337.75</p>

Source: Section 1.4.1, p34 of the submission; and Table 5, p17 of the ratified PICO Confirmation

During the evaluation, it was noted that the wording of the original MBS item descriptor with respect to pathogenic *EGFR* variant testing had changed, to specify access to specific TKIs, and that the testing requirement for access to pembrolizumab had been omitted. Revised wording for the proposed MBS item descriptor is highlighted below.

Table 2 Revised proposed MBS listing, as amended by the ESCs

Category 6 – PATHOLOGY SERVICES
<p>73337</p> <p>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:</p> <ol style="list-style-type: none">if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to an EGFR tyrosine kinase inhibitor under the Pharmaceutical Benefits Scheme are fulfilled; orif the requirements relating to EGFR status for access to immunotherapies listed under the Pharmaceutical Benefits Scheme are fulfilled; orif the requirements relating to Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C variant status for access to sotorasib under the Pharmaceutical Benefits Scheme are fulfilled <p>Fee: \$397.35 Benefit: 75% = \$298.05 85% = \$337.75</p>

Source: Table of the submission; and Table 5 of the ratified PICO Confirmation; *with amendments by the ESCs in bold*

As a result of a survey of laboratories to elicit cost information for this application the applicant has not proposed a change to the MBS fee. This is consistent with the approach adopted in the similar MSAC Application 1617 (inclusion of B-rapidly accelerated fibrosarcoma [*BRAF*] V600 testing in MBS item code for at sarcoma oncogene [*RAS*] testing for colorectal cancer) supported by MSAC at the March 2021 meeting.

PASC noted that testing for the *KRAS* G12C variant could easily report on other pathogenic *KRAS* variants, which would lead to a reduction in the number of patients undergoing *ALK* and *ROS1* FISH testing due to the mutual exclusivity of pathogenic variants.

The submission indicated that this should be simple to implement as pathogenic *KRAS* variant detection using NGS already occurs in most Australian diagnostic laboratories. The fact that all pathogenic *KRAS* variants occur at one of three codons: codon 12, codon 13, and rarely at codon 61 simplifies NGS *KRAS* variant identification. Thus, identifying all pathogenic *KRAS* variants for the purpose of a reduction of the number of *ALK* and *ROS1* FISH tests should be achievable under the proposed fee for the modified MBS item 73337.

The commentary noted that approximately 30% of patients with non-squamous NSCLC will have a pathogenic *KRAS* variant. Thus, if NGS was conducted before IHC testing, the need for triage IHC testing for *ALK* or *ROS1* rearrangements (present in approximately 3% and 1.2% of patients, respectively) would reduce by approximately one third, and fewer patients would consequently require FISH testing. This reduction in the use of *ALK* and *ROS1* testing was not considered in the financial estimates presented in the submission. Very few patients with a *KRAS* non-G12C variant would miss out on treatments targeted to *ALK* or *ROS1* rearrangements as the co-occurrence rate with pathogenic *KRAS* variants ranges from 0–0.2%.

7. Summary of public consultation feedback/consumer issues

The Department received targeted consultation feedback for the PICO confirmation from:

- The Lung Foundation Australia (LFA)
- 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 rebiopsy, 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).

Prior to ESCs consideration (and subsequent to PASC), targeted consultation feedback was received from 5 health professional organisations and one individual:

- Australian Pathology (AP)
- Public Pathology Australia (PPA)
- Australian Genomics (AG)
- Royal College of Pathologists of Australasia (RCPA)
- Omico: Australian Genomic Cancer Medicine Centre.

The consultation feedback collectively supported the MBS funding of *KRAS* G12C variant testing which would enable patient access to early testing and detection of the disease. This in turn would lead to possible resection or provide targeted therapy to patients suitable for second line sotorasib treatment of NSCLC to extend the life expectancy and improve patient outcomes.

PPA and AP stated that *KRAS* is a known marker of clinical benefit in relation to NSCLC which has been well established as part of the clinical pathway and the addition of *KRAS* G12C variant testing (and the companion therapeutic) has the potential to improve the outlook for patients who do not have a targetable mutation in *EGFR*. Further, AP highlighted the proposed intervention would enable prompt therapeutic decision-making by allowing the molecular characterisation of a tumour to be performed as a multiplexed investigation (i.e. covering multiple potential mutations) on the primary tissue sample (wherever possible), and which is pathologist determinable.

The individual consultation feedback indicated that some laboratories across Australia rely on single gene testing platforms and *KRAS* testing is not routinely done in these settings. The individual feedback highlighted that the proposed intervention would ensure the consistency of *KRAS* testing across all or at least most molecular laboratories.

The following considerations were raised in the consultation responses:

- *Disadvantages of the proposed medical service*

PA considered that the testing of a second tissue sample to determine the patient's eligibility for the companion therapeutic would incur risk and discomfort (and also cost to the healthcare system). This potential disadvantage could be addressed if the test were performed on the initial tissue sample.

- *Place in proposed intervention and associated interventions*

AG considered that more clarity is required regarding the type of testing (whether NGS or PCR) offered in this application as there are implications given the often-limited nature of tumour tissue. Further, Omico, AP and RCPA raised whether panel-based testing ought to be considered as an alternative to single gene testing given the cumulative costs of single gene testing for *KRAS*, *ALK*, *ROS*, and *EGFR*.

The RCPA noted that the applicant incorrectly stated that *ALK*, *ROS1* and PD-L1 testing is performed sequentially once a negative test result is found for the previously performed biomarker. The RCPA stated that this is not in line with current clinical practice, safe tissue stewardship or best patient care. Pathologists perform all IHC tests up front at the time of diagnosis of non-squamous NSCLC to preserve tissue and to prevent delays in test results (*ALK*, *ROS1* and PD-L1 IHC). These results are available faster than *EGFR* testing and if a negative *EGFR* result is found and *ALK* IHC or *ROS1* IHC is positive, then confirmatory FISH testing is performed.

The RCPA also noted that the current MBS item numbers for *ALK* and *ROS1* require a negative *EGFR* test result prior to performing FISH, recognising these alterations are essentially mutually exclusive. *KRAS* mutations are more common in NSCLC than *EGFR* and are also mutually exclusive with *EGFR*, *ALK* and *ROS1* alterations. The RCPA indicated that if *KRAS* testing is introduced, there may be a need to alter the *ALK* and *ROS1* item descriptors (73341 and 73344, respectively) to state that both *EGFR* and *KRAS* should be negative prior to proceeding with FISH. This would reduce unnecessary FISH testing

- *Proposed MBS item descriptor*

All organisation feedback received supported the proposed MBS item descriptor in principle. Further, AG noted that that in application 1660 (MET proto-oncogene, receptor tyrosine kinase [MET]ex14 testing in NSCLC), both pathology and genetic services were named and suggested that genetic services should also be added to the current item descriptor. Additionally, AG considered that further details concerning minimum requirements for testing (either NGS or PCR based) would be beneficial.

The individual consultation feedback did not support the proposed MBS item descriptor, stating that it is unclear whether a laboratory using multigene assay on NGS would make a single claim for both *EGFR* and *KRAS*, or whether laboratories performing single gene tests would claim *EGFR* and *KRAS* separately.

- *Proposed MBS fees*

AG agreed with the proposed MBS fees in principle, however, suggested that further cost estimates from overseas be obtained to guide the fee of \$397.35. AG noted that there is also no reference to the differences between PCR and NGS technologies, and possible downstream health economics of each respective method.

In contrast, AP, PPA and RCPA did not agree with the applicant's proposal of using the current MBS item and fee for *EGFR* testing (73337) to also cover *KRAS* testing. These organisations collectively expressed that if an NGS panel (or other panel-based approach such as mass spectroscopy) that includes *EGFR* and *KRAS* is used, there is no increased cost in consumables. However, the extra costs associated with reporting *KRAS* results, validating *KRAS* testing in NSCLC specimens and ongoing participation in additional QAPs is not covered by simply using the current *EGFR* item and fee. The fee would need to be increased if the current *EGFR* item were to be used in a modified format.

AP considered that there should be an MBS fee of \$700 (85% equals ~\$600 rebate) for a panel of at least five hotspot mutations in any of a variety of cancers. The

mutations would need to be specified (and updated) for each tumour type. The laboratory could then run a single test that encompasses all of the mutations across all tumour types for this amount – and in this way there would be explicit recognition of the cost of multiplexing, cost-efficient testing from Medicare’s perspective, and simpler management of the primary systemic therapy.

The RCPA noted that there are also laboratories performing single gene *EGFR* testing and they would be unable to perform a separate single gene *KRAS* assay with no additional fee being provided to cover the test, leading to inequity in patient access to results and subsequent treatment. The RCPA noted that the costs of single gene tests are more expensive than panel testing mainly due to the inability to batch samples thereby not benefitting from a “shared assay” approach. The RCPA stated that a logical approach (that also takes into account multiple other emerging markers in NSCLC) is to introduce a new NGS multigene panel fee for non-squamous NSCLC covering up to 4 oncogene targets that can harbour mutations (*EGFR*, *KRAS*, *BRAF* and *MET*) and a separate NGS fusion panel fee for non-squamous NSCLC covering up to 4 oncogenic fusion targets (*ALK*, *ROS1*, rearranged during transfection [*RET*], neurotrophic tyrosine receptor kinase [*NTRK*]) if no mutations were found with the first panel.

- *The potential additional utilisation of 73337 for patients doing catch-up testing (previously tested for EGFR activating mutations using MBS item 73337, requiring retesting for KRAS G12C variants)*

Although AP and PPA indicated that there is potential additional utilisation of 73337, PPA added that it is not anticipated that a large volume of catch-up testing would be required as it is currently part of the standard of care. AP stated that the “legacy” caseload would be limited to patients who are still alive once the test is listed e.g. all patients who had had uninformative testing using 73337 within the preceding 12 months. This would amount to 75-85% of patients (depending on ethnic background). Within that group, some laboratories will have tested with a panel that includes *KRAS* G12C, even if that result had not been reported; these patients would not require retesting. Both AP and PPA indicated that patients tested by laboratories that are not already doing the *KRAS* test for NSCLC would need to be tested.

- *Proportion of services performed using NGS or PCR for MBS item 73337, and whether the NGS panels are standard or customised (small gene panel or comprehensive genomic profiling)*

AP indicated that most laboratories would use multiplexed assays by NGS or tandem mass spectroscopy and that there would be little comprehensive cancer genome profiling. Similarly, AG stated that although PCR based *therascreen KRAS* RGQ PCR kit (Qiagen) is offered as an option for *KRAS* testing, most Australian laboratories utilise NGS technologies (e.g. a multigene capture panel) for MBS item 73337 which provides a degree of flexibility for future analysis.

PPA indicated that most services utilise NGS and PCR as both technologies have their place. However, PPA emphasised the advantage of PCR as it delivers more rapid focussed results and that NGS may not provide a result if the sample has low DNA yield which would require the sample to be rerun on a RT-PCR assaying, incurring additional costs.

- *Numbers for services provided by MBS item 73337 that require retesting e.g. if insufficient tumour tissue is left in the FFPE tissue blocks or if insufficient DNA is extracted from the tumour tissue in the biopsy, or if DNA testing is inconclusive*

AP indicated that its members have reported that less than 1% assays fail because of inadequate DNA (quantitatively or qualitatively) leading to actual assay failure. Approximately 3-5% of samples do not have sufficient tumour in the sections provided and would not proceed to testing. In some cases, there may be tumour in other blocks from the biopsy. Hence, approximately 2-3% of cases would be repeated on another DNA extraction (same or new block), depending on the assay used; and most of these would produce a result. In contrast, the PPA reported a higher proportion of retesting rates of 5-15%.

- *Numbers for services provided by MBS item 73337 that require rebiopsy e.g. test failure due to inadequate biopsy sample*

AP indicated that 2-3% of services provided by MBS item 73337 require rebiopsy. PPA indicated that small volumes of rebiopsies may be required for various reasons, however, a numeric value of such incidences were not provided.

8. Proposed intervention's place in clinical management

The target population who would be eligible for testing are patients with a diagnosis of NSCLC that is of either non-squamous (adenocarcinoma, adenosquamous carcinoma, and large cell carcinoma) or NOS histology, which will be collectively referred to as non-squamous NSCLC.

Pathogenic variants in the *KRAS* gene are the most common activating alteration in western countries, and are present in approximately 30% of lung adenocarcinomas and 4% of squamous cell carcinomas. In the CodeBreak 100 study, only 1 patient (0.8%) with squamous NSCLC was enrolled compared with 6% in the docetaxel arm of the SELECT-1 trial.

KRAS G12C is the most common of the pathogenic variants and is present in 12.5%–14.5% of non-squamous NSCLC and 1.7%–1.9% of squamous NSCLC.

KRAS G12C variant testing is proposed to occur concurrently with pathogenic *EGFR* variant testing at initial diagnosis of non-squamous NSCLC. In the majority of diagnostic laboratories in Australia an NGS test would be used to analyse the presence of pathogenic variants in both *EGFR* and *KRAS*.

There would be no requirement for additional biosampling if adequate tissue is available for the original NGS *EGFR* variant test. Treatment with sotorasib, if the *KRAS* G12C variant is present, would not commence until failure of first-line therapy for advanced (stage IIIB/IV) disease. Treatment with sotorasib would displace other potential treatments such as docetaxel until a later-line.

9. Comparator

As the proposed test is used in addition to currently available tests, the comparator is no *KRAS* G12C variant testing.

10. Comparative safety

Adverse events from testing

NGS testing for a pathogenic *EGFR* variant is common practice at diagnosis of non-squamous NSCLC in many Australian laboratories, and in many instances would also include pathogenic *KRAS* variant testing. The commentary noted that patients with insufficient material for the initial NGS analysis would already require an additional biopsy. Thus, the safety of NGS pathogenic *EGFR* variant testing would not change with the addition of *KRAS* G12C variant identification.

In the interim, in the uncommon instance where a tumour sample does not receive NGS panel testing for pathogenic *EGFR* ± *KRAS* variants at diagnosis, and there is insufficient archival FFPE tumour sample available for retesting, a rebiopsy may be required.

Adverse events from changes in management

No formal indirect comparisons were conducted in the submission to determine the relative safety of sotorasib and docetaxel. A meaningful interpretation of the naïve comparison is problematic given its indirect nature and cross trial differences in study design, patient populations, and prior and concomitant treatments received.

SELECT-1 did not report the total number of adverse events (AEs) associated with docetaxel, or AEs that were grade 3 or greater. In the sotorasib single arm study (CodeBreak 100) 70% of patients had an AE and 21% of patients had an AE that was grade 3 or greater.

There were higher AE frequencies in the sotorasib study versus the docetaxel arm (any grade) for diarrhoea (31.7% versus 25.0%) and nausea (19.0% versus 11.0%). The frequencies were lower in the sotorasib arm for fatigue (11.1% versus 17.0%), decreased appetite (4.0% versus 11.0%), asthenia (2.4% versus 9.0%), and rash (0.8% versus 9.0%).

11. Comparative effectiveness

Overview of the evidence base

The approach taken in the submission was to present evidence that has been linked to support the contention that targeting of *KRAS* G12C with sotorasib produced superior clinical outcomes to no *KRAS* variant testing plus docetaxel.

Table 3 Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical trials
Accuracy and performance of the test (analytical validity)	Concordance with clinical utility standard	<input checked="" type="checkbox"/> k=1 n=81	High risk of bias
	Concordance between two NGS programs	<input checked="" type="checkbox"/> k=1 n=230	High risk of bias
	Diagnostic yield studies	<input checked="" type="checkbox"/> k=8 n=2,247	High risk of bias for patient selection Low risk of bias for the NGS test
Prognostic evidence	Comparison of outcomes in patients receiving usual care conditioned on the presence or absence of biomarker positive status	<input checked="" type="checkbox"/> k=13 n=9,419	Overall low-moderate risk of bias
Change in patient management	Evidence to show that biomarker determination guides decisions about treatment with the medicine	<input type="checkbox"/> k=0 n=0	
Treatment effectiveness			
Predictive effect (treatment effect variation)	[Comparison of outcomes in patients with and without the biomarker who receive the medicine or its comparator]	<input type="checkbox"/> k=0 n=0	Unanchored MAIC associated with a high risk of bias
Treatment effect (enriched)	[Single randomised controlled trial of medicine vs usual care in patients that are test positive in both arms]	<input type="checkbox"/> k=0 n=0	
Naïve indirect comparison (unanchored MAIC)	<i>KRAS</i> G12C positive patients from a single arm sotorasib study (CodeBreak 100) and SoC patients from a single arm of a randomised trial in patients with advanced NSCLC who had a pathogenic <i>KRAS</i> variant in the second line setting (SELECT-1)	Sotorasib <input checked="" type="checkbox"/> k=1 n=126 Docetaxel <input checked="" type="checkbox"/> k=1 n=256	

k = number of studies, *KRAS* = Kirsten rat sarcoma viral oncogene homologue; n = number of patients; NGS = next generation sequencing; NSCLC = non-small cell lung cancer; MAIC = matching adjusted indirect comparison; SoC = standard of care
Source: Constructed during the evaluation

There was evidence presented to address most parts of the analytic framework (as outlined in Table 4). However, the evidence presented to show concordance between the clinical utility standard and NGS, the most commonly used method in Australia, was limited to one small study. Similarly, the evidence presented for clinical effectiveness of sotorasib was limited to a naïve comparison between one single arm study using sotorasib and a single arm treated with the comparator, docetaxel, from a randomised trial.

Table 4 Data availability to inform comparisons

Proposed test vs no test	NGS diagnostic yield: 1 comparative (NGS vs NGS) study and 7 non-comparative studies	
Proposed test vs alternative test	NGS vs <i>therascreen KRAS</i> PCR test (clinical utility standard): 1 comparative study	
	Proposed medicine (sotorasib)	Comparator medicine (docetaxel)
Biomarker test positive (<i>KRAS</i> G12C variant)	CodeBreak 100 single-arm study	Docetaxel arm from the SELECT-1 study
Biomarker test negative (<i>KRAS</i> non-G12C and <i>KRAS</i> wild type)	No evidence presented	Docetaxel arm from the SELECT-1 study (included patients with <i>KRAS</i> non-G12C variants)

KRAS = Kirsten rat sarcoma viral oncogene homologue; NGS = next generation sequencing; PCR = polymerase chain reaction
Source: Sections 2B and 2D of the submission, as well as additional data identified during the evaluation

The study reporting concordance between NGS and the clinical utility standard, only enrolled NSCLC patients with a clinical indication for pathogenic *EGFR* variant testing. This clinical indication was not described and may have a different spectrum of patients who were tested compared to those tested in the Australian clinical setting. This may have increased the uncertainty as to whether the results are applicable for the target population in Australia.

The evidence to support the comparative clinical benefit of sotorasib was based on an unanchored ¹matching adjusted indirect comparison (MAIC) between data from the single arm sotorasib study enrolling advanced NSCLC patients with a *KRAS* G12C variant and the single arm SoC (docetaxel) from a randomised trial enrolling advanced NSCLC patients with a pathogenic *KRAS* variant (41% *KRAS* G12C). Unanchored MAICs are associated with a high risk of bias.

Effectiveness (based on linked evidence)

Prognostic evidence

Thirteen studies reported the median progression-free survival (PFS) and/or overall survival (OS) for patients with advanced NSCLC with a *KRAS* G12C alteration and/or the hazard ratio (HR) when compared to patients with either *KRAS* wild type (WT) or other *KRAS* pathogenic variants. All except two studies were of good quality with a low risk of bias.

Whereas some studies (k=6) reported that non-squamous NSCLC patients with *KRAS* G12C variants had better or worse PFS and/or OS than those with either other *KRAS* variants or *KRAS* WT, seven studies showed no significant differences.

Thus, the commentary considered the results presented in the submission and the findings in the evaluation report were inconclusive.

Comparative analytical performance

One study screened *EGFR* and *KRAS* pathogenic variants by targeted NGS and commonly used real-time PCR methods (including the clinical utility standard, *therascreen KRAS* PCR kit and the cobas *KRAS* Mutation Test used in the comparator SELECT-1 trial) to evaluate the feasibility of using targeted NGS for the detection of the variants.

¹ No common comparator arm between studies

The positive percent agreement (PPA) between NGS and the *therascreen KRAS* PCR kit was higher for identifying *KRAS* pathogenic variants (96%) than for *EGFR* (83%), and the PPA was 100% for identifying *KRAS* G12C variants (Table 5).

Table 5 Concordance between *therascreen* PCR kits and NGS for detection of pathogenic *KRAS* and *EGFR* variants

Study	Patients	NGS test	<i>therascreen</i> PCR kits	Concordance	
				<i>KRAS</i>	<i>EGFR</i>
Tuononen et al. (2013)	N=81 FFPE surgical samples from NSCLC. The majority (91.4%) of the patients had adenocarcinoma.	Targeted NGS was performed on samples using Illumina HiSeq2000 sequencer	<i>EGFR</i> mutation status using the <i>therascreen EGFR</i> PCR Kit was determined in NSCLC samples. <i>KRAS</i> mutation status using the <i>therascreen KRAS</i> PCR Kit was determined in 78 of the 81 samples (3 had insufficient DNA).	NGS: 24/78 (30.8%) PCR: 25/78 (32.0%) PPA: 24/25 (96.0%) NPA: 53/53 (100%) Variant NGS:PCR G12C 10:10 G12D 5:6 G12V 7:7 PPA and NPA for <i>KRAS</i> G12C = 100%	NGS: 15/81 (18.5%) PCR: 18/81 (22.2%) PPA: 15/18 (83.3%) NPA: 63/63 (100%)

EGFR = epidermal growth factor receptor; FFPE = formalin-fixed paraffin-embedded; *KRAS* = Kirsten rat sarcoma viral oncogene homologue; NGS = next generation sequencing; NPA = negative percent agreement; NSCLC = non-small cell lung cancer; PCR = polymerase chain reaction; PPA = positive percent agreement
Source: Table 20 of the evaluation report

Eight studies identified during the evaluation reported the diagnostic yield for NGS *KRAS* G12C variant testing.

The commentary considered that as only limited concordance data comparing the *therascreen KRAS* PCR kit with NGS was available (one study), the clinical validity of the test could not be determined accurately. The PPA and NPA values presented in Table 5 were used as “estimated” sensitivity and specificity values. The positive and negative predictive values (PPV and NPV) were calculated using these values plus the prevalence rates determined in the treatment population (non-squamous NSCLC with advanced disease) and the proportion of patients with pathogenic variants based on the diagnostic yield determined in the testing population (patients diagnosed with non-squamous NSCLC at any stage).

The commentary noted that the results indicated that the PPV from was 100% for detecting all *EGFR* and *KRAS* variants, suggesting that few patients with non-squamous NSCLC undergoing NGS to detect pathogenic *KRAS* or *EGFR* variants will be misdiagnosed as false positive. For patients who have a negative test result, only 2–4 out of every 100 will actually have a pathogenic *KRAS* or *EGFR* variant (i.e. would be falsely negative). These results should be interpreted with caution because failure to report any information about sample selection or blinding of test results between tests leaves a high risk of bias in these results.

Prevalence

The median prevalence of pathogenic *KRAS* variants in the NSCLC testing population was determined from eight studies conducted in Europe and the USA. It was calculated to be 37.5% (range 24–49) for any pathogenic *KRAS* variant and 14.5% (range 10–20) for the *KRAS* G12C variant.

The median prevalence of pathogenic *KRAS* variants appears to be slightly higher among the testing population when compared to the treatment population (37.5% versus 30%) but the

difference did not quite reach statistical significance ($p=0.053$). There was also no statistical difference between the median prevalence rates of the *KRAS* G12C variant in these populations (14.5% versus 12.5%; $p = 0.109$).

Change in management in practice

The submission concluded that based on biological plausibility, clinical evidence, and guideline recommendations, the presence of the *KRAS* G12C variant is predictive of response to sotorasib treatment. Given the current lack of effective, targeted treatment options in the proposed patient population, it is expected that *KRAS* G12C variant testing would lead to a strong clinician uptake of sotorasib.

12. Economic evaluation

The submission presented a modelled cost-utility analysis, based on an unanchored matching-adjusted indirect comparison of single-arm studies that compared sotorasib and docetaxel patients with *KRAS* G12C NSCLC (i.e. treatment-only). The submission claimed that due to the high diagnostic performance of *KRAS* variant testing, and with the concurrent conduct of pathogenic *EGFR* variant testing in this population, no increase in NGS utilisation is expected with the PBS listing of sotorasib. Therefore, the testing component of the codependent technologies would not impact the cost-effectiveness of sotorasib. An assessment of whether this approach is reasonable depends on the acceptance of the claims that *KRAS* variant testing will occur with all current *EGFR* variant testing, and that the test method(s) used in practice are highly concordant with the tests used in the CodeBreak 100 and SELECT-1 studies:

- The assumption that testing is associated with no additional cost may not be reasonable. PASC noted that most testing of *KRAS* in Australia is done using NGS with gene panels that include *KRAS*, though also mentioned that some smaller laboratories may still be using single gene testing (1669 Ratified PICO). A survey included in the submission (Appendix 1) of 25 laboratories that represent approximately 85–87% of testing in NSCLC suggests that current *EGFR* variant testing is being performed on NGS panels that would also likely include *KRAS* G12C. It is unclear how the remaining 13–15% of tests are being conducted. The laboratories not included in the survey are likely to be smaller and may not test *EGFR* using NGS. However, because they are smaller, the test throughput is likely to be small, and so while there might be a cost it is also likely to be small.
- While the test most commonly used in practice (NGS) was observed to be highly concordant with the PCR-based tests used in the clinical studies, detection of *KRAS* G12C would still be expected to vary according to sample quality. It is well-known that NGS performed with poor quality or inadequate tumour DNA samples have an increased likelihood of having a false negative result. Thus, false negative results (due to poor quality or inadequate DNA) could occur.

The model did however allow the impact of testing to be explored. Under the base case assumptions of no additional cost and perfect performance of *KRAS* variant testing, the incremental cost-effectiveness ratio (ICER) was unchanged from the treatment-only base case. The resulting incremental cost and outcome estimates reflect sotorasib use only in the proportion of the tested population that have the *KRAS* G12C variant (i.e. 13% of the population that enters the model). The commentary noted, in this analysis, no attrition was

considered between the population eligible for testing and that eligible for treatment. This is of particular relevance given that current pathogenic *EGFR* variant testing (and so the time when *KRAS* variant testing is proposed) can occur at diagnosis of NSCLC and, although a large proportion of NSCLC is diagnosed at later stages, it is not all identified at advanced disease. Nor does this approach take into account attrition due to the inability to receive therapies subsequent to first-line treatment. Attrition, however, would only be relevant if *KRAS* variant testing is associated with an additional cost.

The commentary noted that the modelled implication of a false negative was that the cost of testing would be applied, but that the patient would not receive treatment with sotorasib, and so the costs and outcomes modelled are based on receiving docetaxel treatment, which was considered reasonable. False positives were generally modelled as true negative patients, where only the costs of pre-progression treatment (and associated administration and AEs) varied, however the utility decrement applied for IV administration of the comparator treatment was not changed for the reduced duration of comparator treatment, which was not reasonable. These patients were assumed to incur the cost of sotorasib for one month before subsequently being treated with docetaxel. This approach was not justified, noting changes in a treatment plan may be too soon after one month, given that the median time to objective response in CodeBreak 100 was 1.4 months.

Sensitivity analyses using alternate parameters related to testing were explored in the submission. The results of these analyses, in addition to others performed in the commentary, are presented in Table 6. The commentary noted that given the base case assumptions, the implications of some alternate assumptions related to testing can only be observed through multivariate analyses – such as the effect of the prevalence estimate or the estimate of PPA (which only affect the results when *KRAS* variant testing is associated with an additional cost).

Table 6 Testing-related analyses revised to reflect Guidelines recommended annual discount rate

		Inc. cost (\$)	Inc. QALYs	ICER (\$)	%
	Submission base case (treatment only structure)		0.572	1	
	<i>Test-treat structure base case</i>		0.074	1	
	<i>Test cost (base case: \$397.35 in 0% of patients)</i>				
#1	\$397.35 in 15% of patients		0.074	1	0.8%
#2	\$397.35 in 100% of patients		0.074	1	5.6%
	<i>Prevalence of G12C (base case: 13%)</i>				
#3	#1 + 10% KRAS G12C prevalence estimate		0.057	1	1.1%
#4	#1 + 15% KRAS G12C prevalence estimate		0.086	1	0.7%
#5	#1 + 20% KRAS G12C prevalence estimate		0.114	1	0.5%
	Test performance (base case: 100% agreement of NGS and PCR)				
#6	#1 + PPA 95%		0.071	1	0.9%
#7	#1 + PPA 98%		0.073	1	0.9%
#8	NPA 95%		0.074	1	3.6%
#9	NPA 98%		0.074	1	1.4%
#10	PPA 95%, NPA 95%		0.071	1	3.8%
#11	PPA 95%, NPA 98%		0.071	1	1.5%
#12	PPA 98%, NPA 95%		0.073	1	3.7%
#13	PPA 98%, NPA 98%		0.073	1	1.5%
	<i>Treatment duration in false positives (base case: 4 weeks)</i>				
#14	#9 + 6 weeks		0.074	1	2.1%
#15	#9 + 8 weeks		0.074	1	2.7%
	Multivariate analyses				
	#3 AND #13		0.056	1	3.1%
	#3, #13 AND #14		0.056	1	4.0%
	#3, #13 AND #15		0.056	1	4.8%
	#5 AND #13		0.112	1	1.4%
	#5, #13 AND #14		0.112	1	1.8%
	#5, #13 AND #15		0.112	1	2.2%

Note: Analyses in *italics* text were additional analyses conducted during the evaluation. Analyses were also revised to apply the Guidelines-recommended 5% per annum discount rate.

Source: Adapted during the evaluation from analyses presented in Table 3.46, p191 of the submission, with revisions and additional analyses conducted during the evaluation.

ICER = incremental cost-effectiveness ratio; NGS = next generation sequencing; NPA = negative percent agreement; PCR = polymerase chain reaction; PPA = positive percent agreement; QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

The ICER was insensitive to changes in the parameters relating to testing. The ICER was most sensitive to the application of a test cost in all patients that enter the model (5.6% increase) and cumulative changes in the model around prevalence, test performance, test cost and duration of sotorasib treatment in false positives. The analysis that applies the test cost in all patients that enter the model reflects the wording of the proposed item, which allows for single gene testing of *EGFR* or *KRAS* over a transition period. PASC however did note that this could create an incentive for laboratories to charge twice when both *EGFR* and *KRAS* were tested (1669 Ratified PICO).

13. Financial/budgetary impacts

The submission assumed that as *KRAS* variant testing will occur with pathogenic *EGFR* variant testing, no increase in the utilisation or cost of item 73337 is anticipated with listing of sotorasib. As described above, the commentary noted that some smaller laboratories may still be using single gene testing (1669 Ratified PICO) and the proposed item does allow for single gene testing of either *EGFR* or *KRAS*. However, while there might be an additional cost it is likely to be small.

A reduction in costs to the MBS was estimated on the basis of a reduction in docetaxel chemotherapy administration (MBS item 13950). The commentary considered that the estimated reduction in docetaxel use (and therefore, the use of associated chemotherapy administration) may be an overestimate as i) the uptake rate applied for sotorasib may reflect use in patients that would otherwise not have received docetaxel; and ii) the submission has not considered that docetaxel may be displaced rather than replaced in a proportion of patients.

The estimated net financial implications to the MBS are presented in Table 7.

Table 7 Estimated net financial implications to the MBS

	2022	2023	2024	2025	2026	2027
Change in use of MBS item 73337	0	0	0	0	0	0
Cost of <i>KRAS</i> G12C variant testing to the MBS (\$)	\$0	\$0	\$0	\$0	\$0	\$0
Reduction in services related to docetaxel administration	¹	¹	¹	¹	¹	¹
Reduction in cost to the MBS due to affected services (\$)	²	²	²	²	²	²
Net cost to the MBS (\$)	²	²	²	²	²	²

Source: Table 4.12, p204; and Table 4.15, p206 of the submission.

KRAS G12C = Kirsten rat sarcoma viral oncogene homologue with a glycine-to-cysteine substitution at codon 12.

The redacted values correspond to the following ranges:

¹500 to < 5,000

²\$0 to < \$10 million

The commentary considered that the net cost to the MBS is likely to be an underestimate as the reduction in docetaxel use (and therefore, the use of associated chemotherapy administration) may have been overestimated. Further, *KRAS* variant testing may be associated with additional utilisation relative to current pathogenic *EGFR* variant testing as some small pathology providers may still be using single-gene testing. However, the conclusion of cost savings was not observed to change in sensitivity analyses.

14. Key issues from ESCs to MSAC

ESCs key issue	ESCs advice to MSAC
Concordance with the clinical utility standard	The ESCs noted there was high concordance of next generation sequencing (the most commonly used technique in Australia) with the test used in the Codebreak 100 study (<i>therascreen KRAS</i> polymerase chain reaction [PCR] kit) for the detection of pathogenic <i>KRAS</i> , but the evidence was limited to a single study with small patient numbers.
Prognostic value	The ESCs considered that most studies assessing the prognostic value of <i>KRAS</i> G12C compared with <i>KRAS</i> wild type or other <i>KRAS</i> variants were of low risk of bias and showed no significant differences in progression-free or overall survival.
Codependency	The claim of codependence relies on biological plausibility rather than direct evidence.

ESCs discussion

The ESCs noted that the submission sought to include testing for the Kirsten rat sarcoma viral oncogene (*KRAS*) G12C variant into the existing MBS item 73337 (epidermal growth factor receptor [*EGFR*] testing in patients with non-squamous or not otherwise specified [NOS] non-small cell lung cancer [NSCLC]), to determine eligibility for treatment with sotorasib for the treatment of advanced (stage IIIB/IV) NSCLC. The ESCs noted that no change in the existing MBS fee was proposed as laboratories surveyed by the applicant indicated the current fee covers the cost of panel testing by next generation sequencing (NGS) as the most commonly used technique in Australia. The ESCs considered that the ability for laboratories to absorb the costs of adding *KRAS* testing within the current fee for the *EGFR* MBS item may need to be explored further during implementation following any MSAC support for the amendment to the item.

The ESCs noted the consultation feedback from organisations and one individual and discussed issues for consumers such as the patient discomfort associated with the proportion who may require rebiopsy. The ESCs also noted the consultation feedback stating that it was unclear whether a laboratory using multigene assays or NGS would make a single claim for both *EGFR* and *KRAS*, or whether laboratories performing single gene tests would claim *EGFR* and *KRAS* separately and suggesting an alteration to the *ALK* and *ROS1* item descriptors to state that both *EGFR* and *KRAS* should be negative prior to proceeding with FISH.

The ESCs noted that the comparator for *KRAS* G12C variant testing is no testing, i.e. the MBS item 73337 in its current format without *KRAS* G12C variant testing.

The ESCs noted that testing for a pathogenic *EGFR* variant using NGS is common practice at diagnosis in many Australia laboratories, and in many instances would also include pathogenic *KRAS* variant testing. Patients with insufficient material for the initial NGS analysis would already require an additional biopsy. Thus, the ESCs noted that the safety of NGS pathogenic *EGFR* variant testing would not change with the addition of *KRAS* G12C variant identification. The ESCs therefore considered that it would be rare for this addition to require an additional rebiopsy because it would be rare where a tumour sample would not have received NGS panel testing for pathogenic *EGFR* ± *KRAS* variants at diagnosis, and

there would not be sufficient archival formalin-fixed paraffin-embedded (FFPE) tumour sample available for retesting.

The ESCs noted the disagreement between the commentary and pre-subcommittee response (PSCR) in assessing the prognostic value of *KRAS* G12C compared with *KRAS* wild type or other *KRAS* variants but considered that most studies were of low risk of bias and showed no significant differences on progression-free or overall survival.

The ESCs considered that the rationale for codependency was based on biological plausibility as the Codebreak 100 study only enrolled patients with NSCLC who were *KRAS* G12C positive.

The ESCs noted the high concordance (calculated positive percent agreement [PPA]: 96% and negative percent agreement [NPA]: 100%) between the clinical utility standard (*therascreen KRAS* polymerase chain reaction [PCR] kit) and NGS for the detection of pathogenic *KRAS* (Tuononen et al 2013). The ESCs noted that these results were limited to a single study with small patient numbers, particularly for the G12C variant. In addition, the ESCs noted this study had a high risk of bias due to uncertainties around sample selection and that blinding of the results was not reported. The ESCs recalled that MSAC had previously accepted that concordance need not be demonstrated across NGS methodologies in detecting particular biomarkers, in this case, the *KRAS* G12C variant.

The ESCs noted the median prevalence of pathogenic *KRAS* variants in the NSCLC testing population (patients diagnosed with non-squamous NSCLC at any stage) was 37.5% (range 24%–49%) for any pathogenic *KRAS* variant; and 14.5% (range 10%–20%) for the *KRAS* G12C variant. The median prevalence of all pathogenic *KRAS* variants appears to be slightly higher among the testing population when compared to the treatment population (non-squamous NSCLC with advanced disease) but the difference did not quite reach statistical significance (37.5% versus 30% respectively; $p=0.053$). In addition, there was no statistical difference between the median prevalence rates of the *KRAS* G12C variant between these populations ($p = 0.109$). The ESCs also noted the eight studies providing diagnostic yield data were assessed overall at high risk of bias due to patient selection.

The ESCs noted that the submission's base case economic evaluation did not include the implications of testing as it assumed perfect test performance (i.e. 100% sensitivity and specificity) based on the high concordance of PCR and NGS; and that testing is associated with no additional cost based on that *KRAS* variant testing will occur with all current *EGFR* variant testing using NGS. The ESCs noted that the commentary considered it is well-known that NGS performed with poor quality or inadequate tumour DNA samples have an increased likelihood of having a false negative result. However, the ESCs also noted that a sensitivity analysis showed that the incremental cost-effectiveness ratio (ICER) was insensitive to variation in testing parameters (see Table 6).

The ESCs noted that the submission considered no change in utilisation related to testing and thus no additional cost to the MBS. However, the PSCR acknowledged that there may be a small increase in MBS testing costs from a small number of low throughput laboratories still using single-gene testing which is difficult to quantify and may diminish over time as more laboratories move to NGS. The ESCs also noted that the submission did not quantify any cost offsets associated with a reduction in the use of *ALK* and *ROS1* fluorescence *in situ* hybridization (FISH) testing due to identifying all pathogenic *KRAS* variants which are mutually exclusive of the *ALK* and *ROS1* biomarkers. The ESCs considered that

consideration should be given to amending the related MBS item descriptors (73341 and 73344, respectively) to reflect this consequence. However, the ESCs also considered that offsets from reduced FISH testing would likely be small in magnitude, and offsets associated with reflex immunohistochemical (IHC) testing (typically performed at diagnosis of non-squamous NSCLC) would be unlikely to be realised due to the longer turnaround time of NGS relative to reflex IHC testing.

The ESCs noted that a related application is Application 1634 – *Comprehensive genomic profiling of non-small cell lung cancer tumour tissue specimens using next generation sequencing assays*. This application was considered by PASC in April 2021 and proposes a comprehensive gene panel test for NSCLC biomarkers.

The ESCs noted that MBS items and the access restrictions for use of molecular diagnostics in lung cancer is behind current clinical practice. Consistent with the consultation feedback, the ESCs suggested that small gene panels should be proposed as an option for MSAC consideration in the near future.

15. Applicant comments on MSAC's Public Summary Document

Amgen is pleased with the commitment by MSAC to expeditiously reconsider *KRAS* G12C testing if the PBAC recommends sotorasib. Amgen is continuing to work with the PBAC to secure reimbursement of sotorasib for eligible Australian lung cancer patients.

16. Further information on MSAC

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