



**Australian Government**

**Department of Health**

## **MSAC Application 1669**

# **KRAS G12C variant testing to determine eligibility for PBS-subsidised sotorasib second-line therapy in patients with locally advanced or metastatic NSCLC**

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: [hta@health.gov.au](mailto:hta@health.gov.au)

Website: [www.msac.gov.au](http://www.msac.gov.au)

# PART 1 – APPLICANT DETAILS

## 1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): Corporation name: Amgen Australia ABN: 31 051 057 428 Business trading name: Amgen Australia Pty Ltd
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### Primary contact name: REDACTED

Primary contact numbers Business: REDACTED Mobile: REDACTED Email: REDACTED
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### Alternative contact name: REDACTED

Alternative contact numbers Business: REDACTED Mobile: REDACTED Email: REDACTED
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## 2. (a) Are you a lobbyist acting on behalf of an Applicant?

- Yes
- No

### (b) If yes, are you listed on the Register of Lobbyists?

- Yes
- No

## PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

### 3. Application title

KRAS G12C variant testing to determine eligibility for PBS-subsidised sotorasib second-line therapy in patients with locally advanced or metastatic NSCLC.

### 4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Lung cancer is the fifth most common cancer and leading cause of cancer-related death in Australia with a 5-year survival rate of 19%. Non-small cell lung cancer (NSCLC) accounts for ~85% of cases and is diagnosed at an advanced stage in 60-70% of patients when it is no longer amenable to surgery. Systemic therapy is recommended for unresectable NSCLC with selection of appropriate therapy increasingly guided by molecular biomarkers in a patient's tumour. Pathogenic variants of the Kirsten rat sarcoma (KRAS) gene are the most common in NSCLC occurring in 20-25% of tumours (~13% of all tumours have the KRAS G12C subtype). Evidence shows that patients with the KRAS G12C variant have poor treatment outcomes with existing therapies in second-line or later, and prognosis is similarly as poor as for the overall advanced NSCLC population, highlighting the unmet medical need for these patients.

### 5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

The proposed medical service is tumour testing in patients with non-squamous or not otherwise specified (NOS) histology NSCLC to detect KRAS G12C pathogenic variants that would determine eligibility for PBS-subsidised sotorasib second-line therapy. Tumour testing in this population is established and MBS funded for the detection of epidermal growth factor receptor (EGFR) variants to determine eligibility for the PBS-subsidised EGFR tyrosine kinase inhibitors under MBS item 73337. Most testing in Australia is now done using next-generation sequencing (NGS) with gene panels that include KRAS. The intention of this application is to have specific mention of KRAS G12C testing within a modified code 73337.

### 6. (a) Is this a request for MBS funding?

- Yes  
 No

### (b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

- Amendment to existing MBS item(s)  
 New MBS item(s)

### (c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Item number 73337.

### (d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

- i.  An amendment to the way the service is clinically delivered under the existing item(s)
- ii.  An amendment to the patient population under the existing item(s)
- iii.  An amendment to the schedule fee of the existing item(s)
- iv.  An amendment to the time and complexity of an existing item(s)
- v.  Access to an existing item(s) by a different health practitioner group
- vi.  Minor amendments to the item descriptor that does not affect how the service is delivered
- vii.  An amendment to an existing specific single consultation item
- viii.  An amendment to an existing global consultation item(s)
- ix.  Other (please describe below):

**(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?**

- i.  A new item which also seeks to allow access to the MBS for a specific health practitioner group
- ii.  A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
- iii.  A new item for a specific single consultation item
- iv.  A new item for a global consultation item(s)

**(f) Is the proposed service seeking public funding other than the MBS?**

- Yes  
 No

**(g) If yes, please advise:**

The proposed test will determine eligibility for treatment with sotorasib through the PBS.

**7. What is the type of service:**

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

**8. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):**

- i.  To be used as a screening tool in asymptomatic populations
- ii.  Assists in establishing a diagnosis in symptomatic patients
- iii.  Provides information about prognosis
- iv.  Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v.  Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

**9. Does your service rely on another medical product to achieve or to enhance its intended effect?**

- Pharmaceutical / Biological  
 Prosthesis or device  
 No

**10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?**

- Yes  
 No

**(b) If yes, please list the relevant PBS item code(s):**

Not applicable.

**(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?**

- Yes (please provide PBAC submission item number below)  
 No

This application form is lodged in advance of PBAC consideration of sotorasib. A co-dependent submission is in development with intended lodgement REDACTED for consideration at the REDACTED PBAC meeting. The registration application Sotorasib has been accepted for evaluation under the TGA's provisional pathway process. Initial provisional registration will be based on a phase 2 trial with conversion to full registration once the phase 3 trial is completed. Sotorasib has also received TGA orphan designation.

**(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?**

Trade name: LUMAKRAS™

Generic name: Sotorasib

**11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?**

Not applicable

Yes

No

**(b) If yes, please provide the following information (where relevant):**

Not applicable

**(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?**

Yes

No

**(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?**

Yes

No

**(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):**

Not applicable

**12. Please identify any single and / or multi-use consumables delivered as part of the service?**

Molecular pathology service providers in Australia use either NGS or PCR-based methods for KRAS pathogenic variant testing, which use multi-use and single use consumables. Pathology laboratories use standard single-use consumables for both NGS and PCR-based assays, including those for DNA extraction and quantification. Multi-use reagents used in NGS assays include those necessary for DNA extraction, purification and amplification, sample enrichment and library preparation. Library sequencing is performed on a commercially available sequencing platform which in Australia includes those manufactured by Illumina or ThermoFisher Scientific. Single gene testing performed by PCR-based methods require KRAS kits for each specific platform as well as the sequencing platform itself e.g., *therascreen*® KRAS RGQ PCR Kit (Qiagen), *Idylla*™ KRAS Mutation Test (Biocartis) and *cobas*® KRAS Mutation Test (Roche Diagnostics). Both NGS and PCR-based assays require the use of consumables and infrastructure for the archiving of both the sequencing data and the tumour tissue specimens, which would be as per the operations requirements for Australian pathology laboratories.

## PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: In-vitro diagnostic test

Manufacturer's name: Various, this application is not limited to a specific manufacturer.\*

Sponsor's name: Not applicable to the test.

\*The proposed medical service, KRAS G12C pathogenic variant testing, does not specify any particular methodology or test platform. Any appropriately accredited and validated KRAS gene test methodology is within the scope of this application. Molecular pathology service providers in Australia currently use a number of NGS platforms including those manufactured by Illumina and ThermoFisher Scientific. These NGS platforms 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. Additionally, panels for both these platforms can be customised so they may be very simple to just include the EGFR, KRAS and BRAF genes. For those molecular pathology service providers performing single gene testing via PCR-based methods, there are several different commercially available KRAS gene test kits, such as the Idylla™ KRAS Mutation Test (Biocartis), the *therascreen*® KRAS RGQ PCR Kit (Qiagen) and the cobas® KRAS Mutation Test (Roche Diagnostics). The *therascreen*® KRAS RGQ PCR Kit (Qiagen) is the evidentiary standard used in the sotorasib clinical trials.

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

- Class III  
 AIMD  
 N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

- Yes (If yes, please provide supporting documentation as an attachment to this application form)  
 No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

- Yes (if yes, please provide details below)  
 No

ARTG licence numbers for IVDs include but are not limited to:

Bio-Rad Laboratories Pty Ltd - Acquired genetic alteration IVDs

ARTG ID: 316116

Product name: Acquired genetic alteration IVDs

Sponsor: Bio-Rad Laboratories Pty Ltd

Manufacturer: Bio-Rad Laboratories Inc

Sysmex Australia Pty Ltd - Acquired genetic alteration IVDs

ARTG ID: 315997

Product name: Acquired genetic alteration IVDs

Sponsor: Sysmex Australia Pty Ltd

Manufacturer: Sysmex INOSTICS GmbH

Key Diagnostics Pty Ltd - Acquired genetic alteration IVDs

ARTG ID: 270292

Product name: Acquired genetic alteration IVDs

Sponsor: Key Diagnostics Pty Ltd

Manufacturer: ViennaLab Diagnostics GmbH

Agilent Technologies Australia Pty Ltd - Acquired genetic alteration...

ARTG ID: 264573

Product name: Acquired genetic alteration IVDs

Sponsor: Agilent Technologies Australia Pty Ltd

Manufacturer: Dako Denmark AS

Abacus dx Pty Ltd - Acquired genetic alteration IVDs

ARTG ID: 262298

Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs

Sponsor: Abacus dx Pty Ltd

Manufacturer: Biocartis NV

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

Vela Diagnostics Australia Pty Ltd - Acquired genetic alteration IVDs

ARTG ID: 235394

Product name: Acquired genetic alteration IVDs

Sponsor: Vela Diagnostics Australia Pty Ltd

Manufacturer: Vela Operations Singapore Pte Ltd

Vela Diagnostics Australia Pty Ltd - Acquired genetic alteration IVDs

ARTG ID: 228024

Product name: Acquired genetic alteration IVDs

Sponsor: Vela Diagnostics Australia Pty Ltd

Manufacturer: Vela Operations Singapore Pte Ltd

Qiagen Pty Ltd - Acquired genetic alteration IVDs

ARTG ID: 226453

Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs

Sponsor: Qiagen Pty Ltd

Manufacturer: Qiagen GmbH

Qiagen Pty Ltd - Acquired genetic alteration IVDs

ARTG ID: 214994

Product name: Acquired genetic alteration IVDs

Sponsor: Qiagen Pty Ltd

Manufacturer: Qiagen Manchester Ltd

Roche Diagnostics Australia Pty Limited - Acquired genetic alteration IVDs

ARTG ID: 192395

Product name: Acquired genetic alteration IVDs

Sponsor: Roche Diagnostics Australia Pty Limited

Manufacturer: Roche Diagnostics GmbH

Roche Diagnostics Australia Pty Limited - Acquired genetic alteration IVDs

ARTG ID: 192394

Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs

Sponsor: Roche Diagnostics Australia Pty Limited

Manufacturer: Roche Diagnostics GmbH

Roche Diagnostics Australia Pty Limited - Acquired genetic alteration IVDs

ARTG ID: 180933

Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs

Sponsor: Roche Diagnostics Australia Pty Limited

Manufacturer: Roche Diagnostics GmbH

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

**15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?**

- Yes (please provide details below)  
 No

Not applicable

**16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?**

- Yes (please provide details below)  
 No

The evidentiary standard – the *therascreen*<sup>®</sup> KRAS RGQ (Rotor-Gene Q) PCR Kit (Qiagen) - is not yet registered as a companion diagnostic test for sotorasib in NSCLC. The *therascreen* kit is a real-time qualitative PCR assay used in the RGQ molecular diagnostic (MDx) instrument for the detection of seven somatic pathogenic variants in the human KRAS oncogene, using DNA extracted from formalin fixed paraffin embedded (FFPE) tumour biopsy samples (ARTG Entry: 226453). In REDACTED, Qiagen Australia will submit a TGA application for the registration of the *therascreen* KRAS RGQ PCR Kit 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.



## PART 4 – SUMMARY OF EVIDENCE

17. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words) **	Website link to journal article or research (if available)	Date of publication***
1.	Non-randomised trial	Amgen study number 20170543; CodeBreak 100.  Hong DS, Fakih MG, Strickler JH, et al. KRAS <sup>G12C</sup> inhibition with sotorasib in advanced solid tumors. New England Journal of Medicine 2020 Sep 20.  Associated with NCT03600883.	<b>Phase 1</b> , dose ranging component of phase 1/2 sotorasib trial. Study completed.  59 patients with advanced KRAS G12C variant NSCLC who had failed ≥ 2 prior lines. Objective response rate of 32.2% in 19 patients on 960mg/day. No dose-limiting toxicities.  Used to demonstrate predictive validity of KRAS G12C.	<a href="https://nejm.org/doi/10.1056/NEJMoa1917239">https://nejm.org/doi/10.1056/NEJMoa1917239</a>	Published September 20, 2020.
2.	Non-randomised trial¶	Amgen study number 20170543; CodeBreak 100.  PS01.07 CodeBreak 100: Registrational Phase 2 Trial of Sotorasib in KRAS p.G12C Mutated Non-small Cell Lung Cancer.  Proceedings of the 2020 World Conference on Lung Cancer, presented 30 <sup>th</sup> January 2021. ¶  Associated with NCT03600883.	<b>Phase 2</b> , component of phase 1/2 sotorasib trial. Study completed.  126 patients with advanced KRAS G12C variant NSCLC who had failed prior therapy. Objective response rate of 37.1% and median duration of response of 10 months.# No dose limiting toxicities.  Used to demonstrate predictive validity of KRAS G12C.	<a href="https://www.library.iaslc.org/conference-program">https://www.library.iaslc.org/conference-program</a>	Presented January 30, 2021.  Peer review publication expected in Apr/May 2021
3.	Pre-clinical trial	Canon J, Rex K, Saiki AY, et al. The clinical KRAS (G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature 2019;575:217-223  Associated with NCT03600883.	Pre-clinical sotorasib trial.  Sotorasib led to regression of KRAS G12C variant solid tumours and improved anti-tumour efficacy of chemotherapy and targeted agents. No effect on KRAS G12V tumour growth.  Used to demonstrate predictive validity of KRAS G12C.	<a href="https://www.nature.com/articles/s41586-019-1694-1">https://www.nature.com/articles/s41586-019-1694-1</a>	Published 30 October, 2019

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words) **	Website link to journal article or research (if available)	Date of publication***
4.	Drug annotation study	Lanman B, Allen JR, Allen JG, et al. Discovery of a covalent inhibitor of KRAS G12C (AMG510) for the treatment of solid tumors. J Med Chem 2020;63:52-65 Associated with NCT03600883.	Outline of development of sotorasib so as to specifically and irreversibly inhibit KRAS G12C by its unique engagement with a cryptic previously unexploited pocket within G12C. KRAS G12C then trapped in its inactive form, resulting in anti-tumour effects.  Used to demonstrate predictive validity of KRAS G12C.	<a href="https://pubs.acs.org/doi/10.1021/acs.jmedchem.9b01180">https://pubs.acs.org/doi/10.1021/acs.jmedchem.9b01180</a>	Published December 10, 2019
5.	Observational study	Cui W, Franchini F, Alexander M, et al. Real world outcomes in KRAS G12C mutation positive non-small cell lung cancer. Lung Cancer 2020;146:310-317	An Australian study demonstrating that overall survival in KRAS-variant NSCLC, including KRAS G12C, was as poor as KRAS-wild type NSCLC. Also reports prevalence of 29% of KRAS variants in NSCLC population, including 45% KRAS G12C.  Used to support understanding of poor prognosis of KRAS pathogenic variant NSCLC.	<a href="https://doi.org/10.1016/j.lungcan.2020.06.030">https://doi.org/10.1016/j.lungcan.2020.06.030</a>	Published June 26, 2020.
6.	Prospective multicentre study	El Osta B, Behera M, Kim S, et al. Characteristics and outcomes of patients with metastatic KRAS-mutant lung adenocarcinomas: the lung cancer mutation consortium experience. J Thorac Oncol 2019;14:876-889	A prospective multicentre study in which retrospective analyses demonstrated that overall survival in KRAS-variant NSCLC was slightly shorter compared to KRAS-wild type NSCLC, with no differences found between the three main KRAS variant subtypes, including KRAS G12C.  Used to support understanding of poor prognosis of KRAS pathogenic variant NSCLC.	<a href="https://doi.org/10.1016/j.jtho.2019.01.020">https://doi.org/10.1016/j.jtho.2019.01.020</a>	Published February 5, 2019
7.	Prospective cohort study	Jeanson A, Tomasini P, Souquet-Bressand M, et al. Efficacy of immune checkpoint inhibitors in KRAS-mutant non-small cell lung cancer (NSCLC). J Thorac Oncol 2019;14:1095-1101	A prospective cohort study in which retrospective analyses demonstrated that overall survival in KRAS-variant NSCLC was as poor as KRAS-wild type NSCLC, with no differences found between the different KRAS variants including KRAS G12C.  Used to support understanding of poor prognosis of KRAS pathogenic variant NSCLC.	<a href="https://doi.org/10.1016/j.jtho.2019.01.011">https://doi.org/10.1016/j.jtho.2019.01.011</a>	Published February 6, 2019

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words) **	Website link to journal article or research (if available)	Date of publication***
8.	Study of diagnostic accuracy <sup>##</sup>	Sherwood JL, Brown H, Rettino A, et al. Key differences between 13 KRAS mutation detection technologies and their relevance for clinical practice. #  ESMO Open 2017;2:1-12	A comparative study using NSCLC cell lines investigating diagnostic accuracy of 13 KRAS variant detection platforms. <i>therascreen</i> <sup>®</sup> KRAS RGQ PCR kit (Qiagen) compared favourably to NGS in terms of limit of detection, sensitivity and specificity.  Used to demonstrate high diagnostic accuracy of NGS and PCR tests for detecting KRAS G12C.	<a href="https://esmoopen.bmi.com/content/2/4/e000235">https://esmoopen.bmi.com/content/2/4/e000235</a>	Published January 3, 2018
9.	Study of diagnostic accuracy <sup>##</sup>	Tuononen K, Maki-Nevala S, Sarhadi VK, et al. Comparison of targeted next-generation sequencing (NGS) and real-time PCR in the detection of EGFR, KRAS and BRAF mutations on formalin-fixed, paraffin-embedded tumor material of non-small cell lung carcinoma – superiority of NGS.#  Genes, Chromosomes & Cancer 2013;52:503-511	A comparative study demonstrating concordance of diagnostic accuracy between NGS and <i>therascreen</i> <sup>®</sup> KRAS qPCR kit (Qiagen) for detecting KRAS variants including KRAS G12C.  Used to demonstrate high diagnostic accuracy of NGS and PCR tests for detecting KRAS G12C in clinical NSCLC samples.	<a href="https://doi.org/10.1002/gcc.22047">https://doi.org/10.1002/gcc.22047</a>	Published January 30, 2013
10.	Literature review	Sherwood JL, Dearden S, Ratcliffe M, Walker J. 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.  J Exp Clin Cancer Res 2015;34:92	This review finds substantial concordance of KRAS pathogenic variants between primary and metastatic NSCLC tumours, concluding that testing of either the primary or metastasis is sufficient to detect KRAS variants.  Used to support testing of either primary or metastatic NSCLC tumours due to consistency of KRAS pathogenic variants.	<a href="https://ieccr.biomedcentral.com/articles/10.1186/s13046-015-0207-9">https://ieccr.biomedcentral.com/articles/10.1186/s13046-015-0207-9</a>	Published September 4, 2015
11.	Observational study	Kris MG, Johnston BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs.  JAMA 2014;311:1998-2006	An observational study investigating NSCLC driver variants including those in KRAS gene which suggests that they are early oncogenic events in tumour development and retained in downstream tumour lineages.  Shows that KRAS variants are early truncal events in NSCLC, supporting upfront KRAS testing.	<a href="https://jamanetwork.com/journals/jama/fullarticle/1872815">https://jamanetwork.com/journals/jama/fullarticle/1872815</a>	Published May, 2014

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words) **	Website link to journal article or research (if available)	Date of publication***
12	Histologic and molecular investigative study	Rekhtman N, Paik PK, Arcila ME, et al. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous cell carcinoma of the lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations.  Clin Cancer Res 2012;18(4):1167-1176	An investigative study finding that EGFR and KRAS pathogenic variants do not occur in lung squamous cell carcinomas but are seen almost exclusively in lung non-squamous histology carcinomas (adenocarcinoma and NSCLC not otherwise specified histology).  Used to support restriction of KRAS G12C testing to non-squamous and NOS histology NSCLC.	<a href="https://clincancerres.aacrjournals.org/content/18/4/1167.long">https://clincancerres.aacrjournals.org/content/18/4/1167.long</a>	Published February, 2012
13	Evidence based guideline	Lindeman NI, Cagle PT, Aisner DL, et al. 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.  J Thorac Oncol 2018;13:323-358	Internationally developed evidence-based guidelines which present literature to show that KRAS and EGFR pathogenic variants and ALK rearrangements are mutually exclusive of each another.  Used to support the mutual exclusivity of KRAS and EGFR variants and ALK rearrangements.	<a href="https://jto.org/article/S1556-0864(17)33071-X/fulltext">https://jto.org/article/S1556-0864(17)33071-X/fulltext</a>	Published January 25, 2018

\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.

\*\*\* If the publication is a follow-up to an initial publication, please advise.

# Data initially presented at the 2020 World Conference on Lung Cancer was of objective response rate of 37.4 % and median duration of response of 8.4 months, which was at a cut-off of date of follow-up of 1 September 2020. An update was provided after 90 days more follow up with a cut-off date of 1 December 2020 which revealed an objective response rate of 37.1% and median duration of response of 10 months.

## The two key studies that address diagnostic accuracy are shown in this table. Note that due to the extensive number of tests that needed to be conducted, the study by Sherwood and colleagues (ESMO Open 2017;2:1-12) used NSCLC cell lines which were diluted to recreate poorly cellular NSCLC clinical samples. Additional supportive studies are planned to be included in the assessment report including: four additional NSCLC studies showing similar high sensitivity, specificity and positive and negative predictive values for other PCR kits to the various NGS platforms used, and three studies in CRC showing that the *therascreen*® KRAS PCR kit (Qiagen) has comparable high sensitivity and specificity and positive and negative predictive values to the various NGS platforms used (Altamari 2013; Darwanto 2017; Gao 2016). Additionally, an updated handbook from Qiagen with further information about diagnostic accuracy of the *therascreen*® KRAS RGQ PCR kit will be included in the assessment report.

**18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). Please do not attach full text articles, this is just intended to be a summary.**

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.	Observational study	Amgen study number 20200097  A retrospective cohort study of patient characteristics and treatment outcomes among patients with KRAS p.G12C mutation-positive advanced non-small cell lung cancer in the Flatiron Health-Foundation Medicine Clinico-Genomics database.	Real-world data in patients with KRAS G12C variant NSCLC treated with standard of care.  REDACTED	N/A	Completed.
2.	Randomised trial.	Amgen study number 2019009; CodeBreak 200.  A study to evaluate the efficacy, safety, and tolerability of sotorasib (AMG 510) compared to Docetaxel in NSCLC patients with KRAS p.G12C pathogenic variant.  Associated with NCT04303780	Phase 3, multicentre, randomised open label, active-controlled, study to compare sotorasib with docetaxel in previously treated locally advanced or metastatic NSCLC patients with KRAS G12C pathogenic variant. Active, recruiting.  Used to determine the relative efficacy and safety of sotorasib vs docetaxel.	<a href="https://www.clinicaltrials.gov">https://www.clinicaltrials.gov</a>	REDACTED
3.	Observational study	Protocol version identifier: 20200238 Version 1.  Prevalence and clinical outcomes of KRAS G12C mutated advanced lung cancer patients in Australia: a multi-centre retrospective study.	An Australian retrospective observational study to determine KRAS G12C variant prevalence, describe patient clinicopathologic characteristics, treatment patterns and outcomes. Will screen an estimated 2400 patients to find those with KRAS G12C variant NSCLC.  Used to determine the prevalence and clinical outcomes of KRAS G12C variant NSCLC.	N/A	August 2021
4.	In vitro pre-clinical trial	Amgen regulatory dossier / Pharmacology written summary  Form-098799: Sotorasib	Pharmacologic investigations and in vitro pre-clinical trials show that sotorasib modified and inhibited KRAS G12C, whilst having minimal effects on KRAS wild-type cell lines or those with other KRAS variants.  Used to demonstrate predictive validity of KRAS G12C.	N/A	Completed

\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

\*\*\*Date of when results will be made available (to the best of your knowledge).

## PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

The Royal College of Pathologists of Australasia (RCPA)

- 20. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

The Medical Oncology Group of Australia (MOGA)

- 21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

Lung Foundation Australia. Amgen contacted this group for a letter of support and were informed that it is their preference to instead have their views solicited by MSAC (or the MSAC Secretariat) rather than the applicant.

- 22. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

Not applicable

- 23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

Name of expert 1: **REDACTED**

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

Name of expert 2: **REDACTED**

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

*Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.*

# PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

## **PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION**

### **24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:**

In Australia in 2020, there were an estimated 13,258 new cases of lung cancer diagnosed, which represents 9.1% of all cancer diagnoses. Lung cancer was the fifth most common cancer diagnosed for males and females in 2020 and was the number one cause of cancer-related mortality with 8641 deaths, accounting for 18% of all cancer deaths (Australian Institute of Health and Welfare 2020).

Lung cancer can be divided into two main subtypes, NSCLC, which represents 85% of all lung cancer cases, and small cell carcinoma. NSCLC comprises a heterogeneous group of tumours, including adenocarcinoma, the most common histologic subtype, squamous cell carcinoma and large cell carcinoma. Adenocarcinoma and large cell carcinoma (or NSCLC, NOS) constitute the non-squamous histologic subtypes. Approximately 30% of NSCLC patients present with localised disease which is potentially amenable to curative surgical resection, while the majority of patients present with advanced disease. It is recognised that approximately 50% of patients with resected NSCLC will relapse or recur within 5 years. In Australia between 2012-2016, lung cancer was associated with a 5-year survival rate of 18.6%, which is poorer than for the other frequently diagnosed cancers including prostate, breast and bowel cancer and melanoma (Australian Institute of Health and Welfare 2020). Five-year survival for lung cancer varies by stage, ranging from 67.7% for stage I, 32.3% for stage II, 17.1% for stage III and 3.2% for stage IV (Australian Institute of Health and Welfare 2020).

NSCLC is also a heterogeneous disease from a genomic standpoint, with a wide variety of genomic subtypes known to drive tumour growth. Pathogenic variants in the KRAS gene are the most prevalent oncogenic driver abnormality in NSCLC, reported in 20-25% of NSCLC in recent Australian series, with about 13% of tumours having the KRAS G12C subtype (Clay 2016; Russell 2017; Tan 2018; Cui 2020). KRAS pathogenic variants are more common in current or ex-smokers and are present predominantly in non-squamous histology i.e., adenocarcinoma, large cell carcinoma and NSCLC, NOS histologies (Russell 2017; Tan 2018; Fong 1998; Rekhtman 2012). KRAS pathogenic variants are mutually exclusive of other recognised oncogenic drivers in NSCLC such as EGFR pathogenic variants and ALK and ROS1 rearrangements (Lindeman 2018).

The KRAS protein functions as a molecular switch in growth factor signalling pathways. It regulates proliferation by alternating between a guanosine diphosphate (GDP)-bound inactive form and a guanosine triphosphate (GTP)-bound active form. The GTP-bound active form of the KRAS protein is able to engage downstream effector proteins which promotes a pro-proliferative response (Mascaux 2005; Nadal 2014; Lanman 2020). Pathogenic variants in the KRAS gene impair the regulated cycling between the active and inactive forms of the KRAS protein, disrupting the inactivation of KRAS which leads to the accumulation of the pro-proliferative form (Lanman 2020). Despite being one of the first oncogenes identified, a clinically useful KRAS inhibitor has not been found. Two features which have influenced the failure to identify a KRAS inhibitor include the very strong affinity between KRAS and GDP and GTP and the lack of deep surface pockets in the KRAS protein. Both of these features have obstructed efforts to develop nucleotide-competitive inhibitors (Lanman 2020).

The prognostic significance of KRAS pathogenic variants in NSCLC is controversial with some studies suggesting that patients with KRAS-mutant NSCLC have shorter overall survival than those with KRAS wild type tumours (Tan 2018; Mascaux 2005; Nadal 2014) whilst others do not (Shepherd 2013). However, three real-world evidence natural history studies conducted by Amgen showed that outcomes in second or later lines of therapy for patients with KRAS *p.G12C*-mutated advanced NSCLC were as poor as the overall patient population with advanced NSCLC. Furthermore three recent prospective studies, one from

Australia, support these findings, demonstrating that patients with KRAS-variant NSCLC, including those with *KRAS p.G12C*-mutated advanced NSCLC, have as poor overall survival as patients with advanced KRAS-wild-type NSCLC (Cui 2020; El Osta 2019; Jeanson 2019).

**25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:**

Staging of NSCLC via clinical means and the usual radiologic investigations and histologic assessment for determination of NSCLC subtype are routine elements in the management of patients with suspected lung cancer. There would not need to be any changes to the routine investigation and work-up of these patients.

As is the case in EGFR gene testing, KRAS gene testing should be restricted to patients with non-squamous or NOS histology NSCLC. This is because KRAS pathogenic variants, like EGFR pathogenic variants, are found predominantly in non-squamous or NOS histology and are very rare in squamous NSCLC (Rekhtman 2012).

Importantly, Amgen proposes that KRAS gene testing for KRAS G12C pathogenic variants be performed at the same time that EGFR gene testing is currently performed, which is at diagnosis or prior to the initiation of treatment in patients with advanced / metastatic non-squamous or NOS histology NSCLC for several reasons as outlined below.

KRAS pathogenic variants are the most frequent molecular abnormality detected in non-squamous or NOS histology NSCLC in Australia, representing 20-25% of molecular abnormalities detected in recent Australian series, with about 13% of tumours having the KRAS G12C subtype (Cui 2020; Russell 2017). This is roughly equivalent to the prevalence rate of 13-14% of EGFR pathogenic variants in the Australian population, with KRAS pathogenic variants also being mutually exclusive of EGFR pathogenic variants and of ALK and ROS1 rearrangements (Lindeman 2018).

Translational studies have shown that KRAS pathogenic variants are an early oncogenic event in NSCLC development (Kris 2014), which do not change over time and are preserved in metastases (Sherwood 2015), so there is no clinical reason to delay testing until consideration of second-line therapy, which is when sotorasib will be used.

The majority of Australian laboratories currently use NGS technology and so are already testing for KRAS pathogenic variants due to its inclusion in targeted NSCLC gene panels, along with EGFR and BRAF pathogenic variants at the very least. Further, for those laboratories using single-gene testing by PCR-based methods, there is a real risk of attrition of tumour tissue if KRAS testing occurs after testing for EGFR pathogenic variants, ALK and ROS1 rearrangements and PD-L1 immunohistochemistry.

Attrition of tumour tissue plus delay in KRAS G12C testing will lead to an increased rate of re-biopsy in NSCLC patients, with attendant risks of biopsy-related morbidity. It is therefore safer for NSCLC patients and more cost-effective to perform KRAS G12C testing prior to the initiation of therapy at the same time as testing for EGFR pathogenic variants occurs, under MBS item 73337.



**26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):**

The current clinical management pathway for patients with suspected lung cancer includes the following (no chart provided as a very simple pathway):

- The patient is referred to and presents to a specialist medical practitioner with suspected lung cancer, after initial presentation to a general practitioner,
- The patient is investigated with radiologic tests including a contrast-enhanced computed tomography (CT) scan to confirm clinical suspicions and to determine the stage of the lung cancer,
- The patient is then referred for biopsy, which is followed by pathologic confirmation / diagnosis of lung cancer and determination of NSCLC subtype,
- If the patient is confirmed to have locally advanced or metastatic non-squamous or NOS histology NSCLC, the treating specialist requests further pathologic investigations on the tumour tissue in the biopsy material, in line with those currently listed on the MBS, to identify genomic alterations so as to determine appropriate PBS subsidised therapy.

The current clinical management pathway outlined above would be the same for patients who would be eligible for KRAS pathogenic variant testing. This is because Amgen proposes that KRAS pathogenic variant testing occur at the same time as EGFR pathogenic variant testing, under MBS item 73337, which currently occurs at diagnosis or prior to initiation of therapy.

**PART 6b – INFORMATION ABOUT THE INTERVENTION:**

**27. Describe the key components and clinical steps involved in delivering the proposed medical service:**

The key components and the clinical steps involved in delivering KRAS G12C pathogenic variant testing in patients with non-squamous and NOS NSCLC histology are the same as those that already exist for EGFR pathogenic variant testing in the same group of patients, under MBS item 73337. It is understood that most Australian laboratories utilise NGS technologies for molecular testing with the remainder of laboratories using single-gene PCR-based methods. The initial steps of extraction, isolation and quantification of tumour DNA from the biopsy specimens is the same for both NGS and PCR methods. The next key steps involved in molecular testing with 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. Of note, NGS panels can be either standard or customised; if customised, an NGS panel can be very simple and include just the KRAS, EGFR and BRAF genes. The next key steps involved in molecular testing with PCR methods include amplification, post-PCR analysis and reporting of test results.

A 2013 study using NSCLC tumour tissue showed that PCR-based methods demonstrated significant concordance with NGS methods (Tuononen 2013). Additionally, however, NGS methods detected rare pathogenic variants in the EGFR gene which were not detected by PCR methods. A more recent study comparing different detection platforms for KRAS pathogenic variants in NSCLC using cell lines demonstrated significant concordance between various PCR-based tests including the Idylla™ KRAS Mutation Test (Biocartis), the *therascreen*® KRAS RGQ PCR Kit (Qiagen) and the cobas® KRAS Mutation Test (Roche Diagnostics) and several NGS platforms, with similar sensitivity and specificity (Sherwood 2017). Again, NGS detected rare and multiple KRAS pathogenic variants whilst the KRAS mutations detected by the PCR-based methods were limited to those included in the pre-designed assays (Sherwood 2017). Similar investigations in metastatic colorectal carcinoma comparing KRAS detection methods including the *therascreen*® KRAS RGQ PCR Kit (Qiagen) made similar findings (Altimari 2013; Darwanto 2017; Gao 2016).

**28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?**

No.

**29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?**

Not applicable.

**30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e., accessibility, dosage, quantity, duration or frequency):**

It is anticipated that most NSCLC patients will require only one KRAS G12C test in their lifetime. This is because KRAS pathogenic variants in NSCLC are known to be stable over time, with substantial concordance reported between primary tumours and metastases, indicating that both primary and metastatic tumour sites are suitable for testing (Sherwood 2015). Additionally, as recommended in international guidelines, highly sensitive diagnostic testing methods are used in Australia to detect KRAS pathogenic variants so as to ensure accuracy of results (Lindeman 2018). Re-testing may be required in a small minority of patients if insufficient tumour tissue is left in the FFPE tissue blocks, if insufficient DNA is able to be extracted from the tumour tissue in the biopsy or if DNA testing is inconclusive.

**31. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:**

Not applicable.

**32. If applicable, advise which health professionals will primarily deliver the proposed service:**

A request for testing for genomic alterations in tumour tissue from patients with non-squamous or NOS histology NSCLC would come from the patient's treating clinician, prior to initiation of therapy. The most likely clinicians making such requests are medical oncologists and thoracic medicine physicians. All steps associated with the conduct of KRAS pathogenic variant testing using either an NGS assay or PCR-based methods will be performed by pathologists and laboratory technicians (Approved Pathology Practitioners in Accredited Pathology Laboratories as defined in the MBS Pathology table) on the request of the treating clinician, with results of testing being reported back to the treating clinician to guide treatment selection.

**33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:**

Not applicable.

**34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:**

Testing would continue to be delivered by Approved Pathology Practitioners in Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

**35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:**

Testing for genomic alterations in tumour tissue from patients with non-squamous and NOS histology NSCLC is already well established and occurring in clinical practice in Australia in both public hospital laboratories and private pathology laboratory networks. Therefore no additional qualifications or formal training would be required for molecular testing either by NGS or PCR-based methods in these laboratories. It must be noted however that all laboratories performing molecular testing whether by NGS or PCR-based methods so as to guide patient management at the initiation of treatment must hold the appropriate accreditations to do so. NGS testing must be performed in line with the standards set out in the "Requirements for human medical genome testing utilising massively parallel sequencing technologies" document (NPACC 2017). Similarly PCR testing must be performed in line with the standards set out in the "Requirements for medical testing of human nucleic acids" document (NPACC 2013). Additionally, both public and private laboratories must submit to audits of testing standards so as to receive accreditation from the National Association of Testing Authorities (NATA) and must also take part in and demonstrate proficiency to the molecular arm of the Quality Assurance Programme run by the College of Pathologists of Australasia.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- Inpatient private hospital (admitted patient)
- Inpatient public hospital (admitted patient)
- Private outpatient clinic
- Public outpatient clinic
- Emergency Department
- Private consulting rooms - GP
- Private consulting rooms – specialist
- Private consulting rooms – other health practitioner (nurse or allied health)
- Private day surgery clinic (admitted patient)
- Private day surgery clinic (non-admitted patient)
- Public day surgery clinic (admitted patient)
- Public day surgery clinic (non-admitted patient)
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

Not applicable

37. Is the proposed medical service intended to be entirely rendered in Australia?

- Yes
- No – please specify below

**PART 6c – INFORMATION ABOUT THE COMPARATOR(S)**

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

**Test:** No testing, i.e., Medicare Benefits Schedule (MBS) item 73337 in its current format, which has no explicit inclusion of KRAS G12C pathogenic variant testing in NSCLC, and no reference to sotorasib.

**Drug:** Docetaxel which is standard of care second-line therapy in patients without a currently actionable biomarker.

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

- Yes (please list all relevant MBS item numbers below)
- No

MBS item 73337.

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

A summary of the current clinical management pathway that patients may follow in which they do not receive KRAS G12C pathogenic variant testing includes (refer to the first flow diagram in attachments section):

- The patient is diagnosed with locally advanced or metastatic non-squamous or NOS histology NSCLC and is suitable for systemic therapy,
- The patient's treating clinician will request testing of the patient's tumour tissue for EGFR pathogenic variants, funded under MBS item 73337,
- If the patient's tumour contains a sensitising EGFR pathogenic variant, the patient will be offered an EGFR tyrosine kinase inhibitor (TKI),
- If the patient's tumour does not have an EGFR pathogenic variant, screening for an ALK rearrangement by ALK immunohistochemistry (IHC) will take place; if there is any positivity with ALK IHC, ALK FISH will be performed, funded under MBS item 73341,
- If the patient's tumour is ALK-rearranged, the patient will be offered an ALK TKI,
- If an ALK rearrangement is not confirmed, the patient's tumour will be screened for ROS1 rearrangement by ROS1 IHC; if there is 2+ or 3+ staining with ROS1 IHC, ROS1 FISH will be performed, funded under MBS item 73344,
- If the patient's tumour is ROS1-rearranged, the patient will be offered a ROS1 TKI,
- If the patient's tumour is negative for EGFR, ALK and ROS1 abnormalities (i.e., the group within which patients with KRAS G12C variant tumours reside), PD-L1 IHC will be performed, and the patient will be offered immunotherapy and/or chemotherapy. At progression, the patient may be offered chemotherapy (mainly docetaxel).

**41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?**

- In addition to (i.e., it is an add-on service)  
 Instead of (i.e., it is a replacement or alternative)

Because it is understood that most Australian laboratories are using NGS technology, most NSCLC patients are already receiving KRAS pathogenic variant testing when their tumours are tested for EGFR pathogenic variants, funded under MBS item 73337. This is due to the parallel testing capability of NGS and due to the fact that many targeted gene panels used for EGFR gene testing in NSCLC include the KRAS gene. So for these laboratories, there will be no change to testing pathways.

For those laboratories using single-gene PCR-based tests, they will need to source and validate a single-gene PCR test for KRAS pathogenic variants which includes the KRAS G12C subtype as part of its pre-designed assay. The other alternative is that laboratories using PCR-based methods may decide to upgrade to NGS technologies. However, in reality, these laboratories will be able to use the KRAS single-gene tests which they are already using for KRAS pathogenic variant testing in metastatic colorectal cancer, as the same subtypes of KRAS pathogenic variants can occur in both NSCLC and metastatic colorectal cancer. So for the labs using PCR-based tests, there may be an additional test performed for NSCLC patients, but this will not result in additional claims for the proposed medical service listed on the MBS schedule.

**(b) If instead of (i.e., alternative service), please outline the extent to which the current service/comparator is expected to be substituted:**

Substitution of the proposed comparator service is expected to be effectively 100%.

**42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):**

A summary of the clinical management pathway that patients may follow in which they do receive KRAS G12C pathogenic variant testing includes (refer to the second flow chart in the attachments below):

- The patient is diagnosed with locally advanced or metastatic non-squamous or NOS histology NSCLC and is suitable for systemic therapy,
- The patient's treating clinician will request testing of the patient's tumour tissue for EGFR and KRAS pathogenic variants, funded under **modified** MBS item 73337,
- If the patient's tumour contains a sensitising EGFR pathogenic variant, the patient will be offered an EGFR tyrosine kinase inhibitor (TKI),

- **If the patient’s tumour contains a KRAS G12C pathogenic variant, the patient will be offered immunotherapy and/or chemotherapy; on disease progression, the patient will be offered sotorasib (instead of docetaxel),**
- If the patient’s tumour does not have an EGFR or KRAS pathogenic variant, screening for an ALK rearrangement by ALK immunohistochemistry (IHC) will take place; if there is any positivity with ALK IHC, ALK FISH will be performed, funded under MBS item 73341 (there may be flow on implications for item 73341 with inclusion of KRAS testing within item 73337),
- If the patient’s tumour is ALK-rearranged, the patient will be offered an ALK TKI,
- If an ALK rearrangement is not confirmed, the patient’s tumour will be screened for ROS1 rearrangement by ROS1 IHC; if there is 2+ or 3+ staining with ROS1 IHC, ROS1 FISH will be performed, funded under MBS item 73344 (there may be flow on implications for item 73344 with inclusion of KRAS testing within item 73337),
- If the patient’s tumour is ROS1-rearranged, the patient will be offered a ROS1 TKI,
- If the patient’s tumour is negative for EGFR, KRAS, ALK and ROS1 abnormalities, PD-L1 IHC will be performed, and the patient will be offered immunotherapy +/- chemotherapy.

**PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME**

**43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):**

The clinical claims are entirely due to the change in pharmaceutical management of patients with KRAS G12C mutated NSCLC and will be expanded in the associated PBAC submission.

**44. Please advise if the overall clinical claim is for:**

- Superiority  
 Non-inferiority

**45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:**

<p><b>Safety Outcomes:</b></p> <p>Incidence of adverse events from subsequent treatment</p> <p>Adverse events associated with biopsy</p> <p>Re-biopsy rate</p> <p>Impact on patients of false positive and false negative test results</p> <p><b>Clinical Effectiveness Outcomes:</b></p> <p>Objective response rate</p> <p>Duration of response</p> <p>Progression free survival</p> <p>Overall survival</p> <p><b>Test related</b></p> <p>Diagnostic accuracy</p> <p>Prognostic accuracy</p> <p>Change in clinical management</p> <p>Test turn-around time</p>
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## PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

### 46. Estimate the prevalence and/or incidence of the proposed population:

Based on projections of lung cancer incidence from the Australian Institute of Health and Welfare (AIHW, 2020), there will be 13,258 new cases of lung cancer in Australia in 2020. Of these, 86.6% will have NSCLC (Mitchell et al 2013) and 74.2% of tumours will have non-squamous NOS histology (Nivolumab PSD November 2016) giving a total incidence pool of 8,519 patients potentially eligible for EGFR/KRAS testing.

Not all patients with locally advanced or metastatic NSCLC will be considered for systemic therapy and subject to EGFR/KRAS testing. In the 2019/20 financial year there were 4,643 claims for EGFR testing under MBS item 73337, representing the approximate number of patients tested. The KRAS G12C variant is present in ~13% of non-squamous/NOS NSCLC tumours. The number of patients in the tested cohort potentially eligible for sotorasib would therefore be 604.

### 47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

The medical service would be undertaken to determine eligibility for treatment with sotorasib. It is anticipated that patients would be tested only once per lifetime, at diagnosis or prior to the initiation of treatment.

### 48. How many years would the proposed medical service(s) be required for the patient?

Not applicable.

### 49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

It is estimated that approximately 5,373 patients will utilise the medical service in Year 1 (2022) based on forecast growth from current utilisation of EGFR testing.

### 50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

Uptake of the proposed medical service is estimated to be consistent with current utilisation of MBS item 73337. A linear regression was used to project the number of services provided under item 73337 from 2020 to 2027 based on the service volumes from 2015 to 2019 (refer table below).

Source	Calendar Year	Services
MBS item report	2015	3,368
	2016	3,419
	2017	3,863
	2018	4,147
	2019	4,603
Projections	2020	4839
	2021	5159
	2022 (year 1)	5479
	2023 (year 2)	5799
	2024 (year 3)	6119
	2025	6438
	2026	6758
	2027	7078

Leakage to populations not targeted by the service will be constrained by the MBS item descriptor to ensure testing is applied only where clinically indicated.

## PART 8 – COST INFORMATION

### 51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

The current fee for EGFR testing under MBS item 73337 is \$397.35. Amgen has spoken with representatives from several laboratories and had mixed feedback as to whether or not this fee is adequate to cover the cost of NGS panel testing across multiple genes. Amgen also notes two MSAC applications in progress relevant to this matter:

- Application 1617 is seeking to add BRAF testing to established RAS testing in metastatic colorectal cancer (i.e. MBS item 73338). The Sponsor of the application has proposed that the fee need not be increased as most testing claimed under this item is with NGS panels that include BRAF. The ratified PICO for the application asks for costing information to be provided: “Additional information, including an average cost from all mCRC genetic panel test providers, should be provided if possible. *PASC noted that there was no proposal to increase the fee for this item.*”
- Application 1634 is seeking MBS funding for comprehensive genetic profiling with NGS, to replace all of the established individual tests in the NSCLC setting. The application form is the only document currently available on the MSAC application page. The Sponsor of this application does not yet propose a fee but acknowledges that costing information needs to be provided. If this application is approved, and a new MBS item established, it would encompass KRAS testing and eclipse the need for a modified item 73337.

Amgen also notes a stalled MSAC Application 1495 from the Royal College of Pathologists Australasia (RCPA) where the cost of a  $\geq 3$  gene panel test was itemised to a total of \$600:

Equipment and resources for $\geq 3$ genes (ISH, PCR, small NGS panel):	
DNA and RNA extraction and quantification	\$30
Kit	\$250
Sequencing	\$150
<u>Labour (medical and scientific) and bioinformatics for interpretation</u>	<u>\$170</u>
TOTAL	\$600

Amgen has struck a challenge in obtaining source test costing information laboratories and would appreciate advice from the MSAC Secretariat on how to address the cost of the test in the MSAC submission. A survey of laboratories was undertaken to elicit cost information for this application form. Sixteen laboratories were approached and seven responded to the survey. An additional laboratory representative was interviewed during development of the survey questions. Six of the 8 laboratories included in the project are using NGS and 2 are using mass spectrometry (one of the latter indicated a move to NGS in the near future). No laboratory was willing to provide detailed cost information to Amgen. One laboratory provided a total cost estimate of \$400 for an NGS panel test. All other survey respondents were unwilling to provide cost information but indicated that the current fee of \$397.35 covered the cost of current NGS testing with small-medium sized panels. Note that the survey does not include the perspectives of laboratories doing single gene testing.

As Amgen’s survey indicates the current fee of \$397.35 may be adequate for testing done using NGS, which represents the majority, this fee has been retained for the purpose of the application form.

### 52. Specify how long the proposed medical service typically takes to perform:

The time taken to perform the proposed medical service of testing for KRAS G12C pathogenic variants depends on the platform used, though batching of specimens occurs in most laboratories which can extend the time taken with all platforms. On the whole though PCR-based platforms take several hours to a day to perform whilst NGS platforms take approximately 3-5 days. The optimal turnaround time between the receipt of a patient’s tumour tissue specimen at the pathology laboratory and availability of results is 5 days, however typical turnaround times are believed to be 10-12 days.

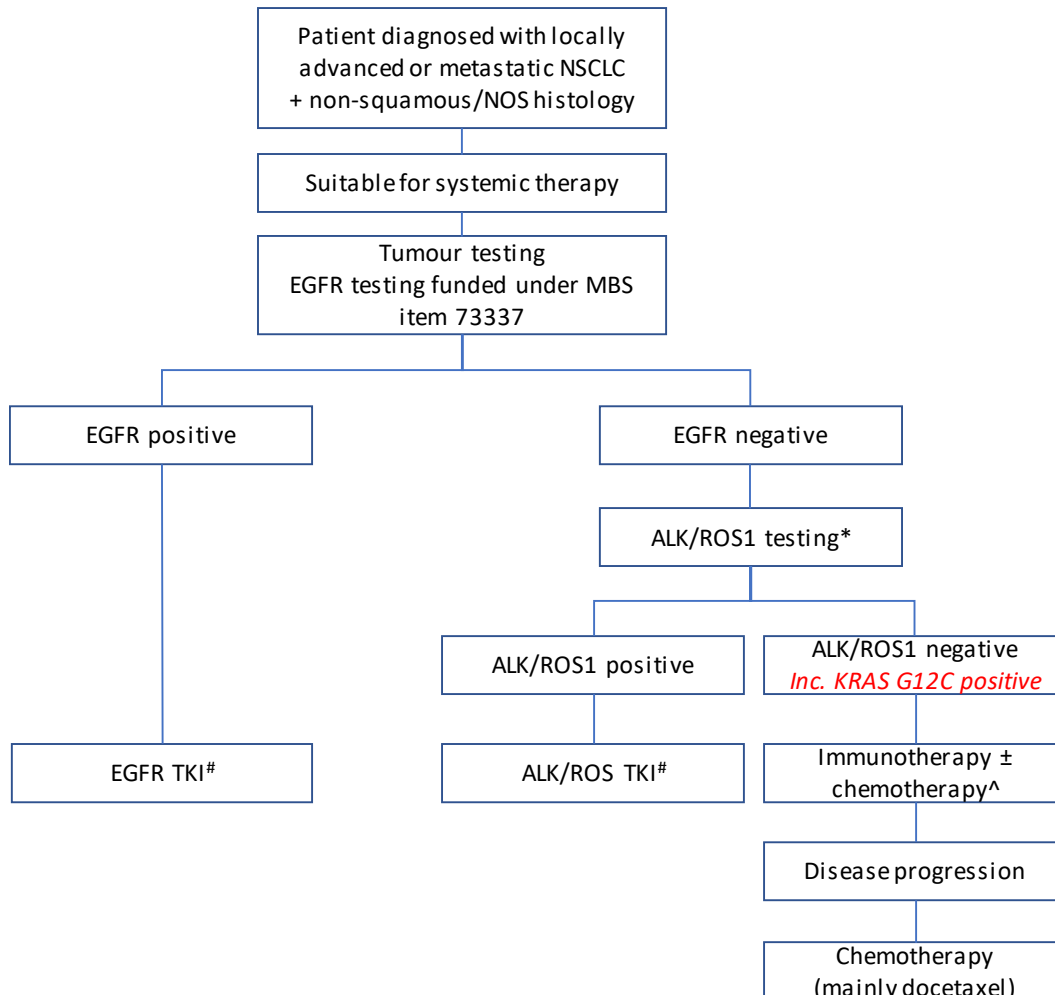
**53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.**

Category 6 – PATHOLOGY SERVICES
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: <ol style="list-style-type: none"><li>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</li><li>2. the requirements relating to Kirsten rat sarcoma oncogene (KRAS) G12C gene status for access to sotorasib under the Pharmaceutical Benefits Scheme are fulfilled.</li></ol> Fee: \$397.35 (unless an alternative cost can be supported)



## Attachments

A flowchart representing the current tumour biomarker testing in NSCLC and the treatment pathway for patients with KRAC G12C variant tumours is provided below (effective March 2021).

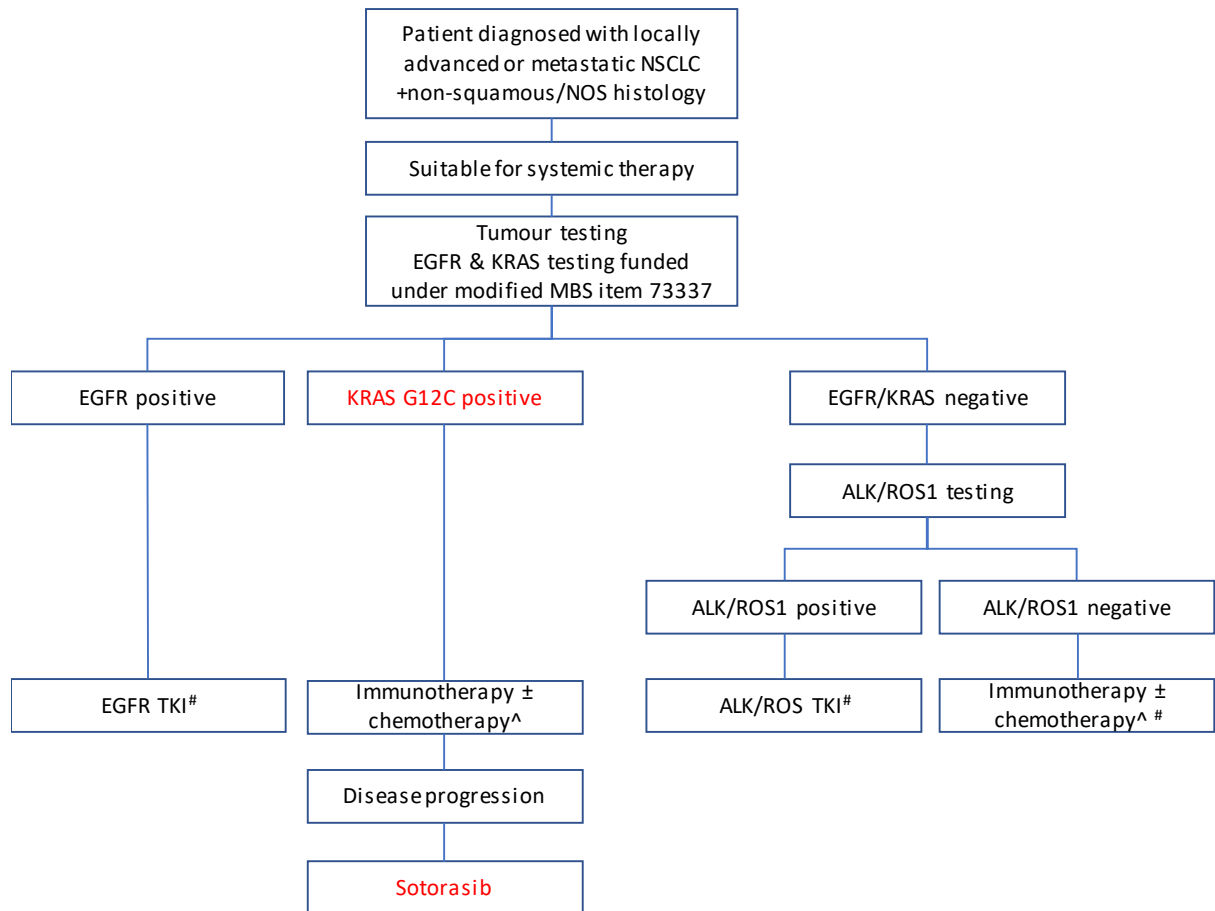


\* Grouped for simplicity but in reality MBS funding is based on sequential ALK then ROS1 testing

^ Main pathway shown for simplicity

# Truncated pathway presented for simplicity as these patient groups would not be eligible for sotorasib

A flowchart representing the future tumour biomarker testing in NSCLC and the treatment pathway for patients with KRAC G12C variant tumours with availability of sotorasib is provided below.



\* Grouped for simplicity but in reality MBS funding is based on sequential ALK then ROS1 testing  
 ^ Main pathway shown for simplicity  
 # Truncated pathway presented for simplicity as these patient groups would not be eligible for sotorasib

## References

- Altimari A, de Biase D, De Maglio G, Gruppioni E, Capizzi, E Degiovanni A, et al. 454 next generation-sequencing outperforms allele-specific PCR, sanger sequencing, and pyrosequencing for routine KRAS mutation analysis of formalin-fixed, paraffin-embedded samples. *OncoTargets and Therapy*. 2013; 6: 1057-1064
- Australian Institute of Health and Welfare 2020. Cancer data in Australia. Web report; updated 13 Nov 2020. Cat. no: CAN 122. Canberra: AIHW (<https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/data>).
- Clay TD, Russell PA, Do H, et al. Associations between the IASLC/ATS/ERS lung adenocarcinoma classification and EGFR and KRAS mutations. *Pathol* 2016; 48: 17-24
- Cui W, Franchini F, Alexander M, et al. Assessing the significance of KRAS G12C mutation: clinicopathologic features, treatments, and survival outcomes in a real-world KRAS mutant non-small cell cancer cohort. *Lung Cancer* 2020; 146: 310-317
- Darwanto A, Hein AM, Strauss S, Kong Y, Sheridan A, Richards D, et al. Use of the QIAGEN genereader NGS system for detection of KRAS mutations, validated by the QIAGEN Therascreen PCR kit and alternative NGS platform. *BMC Cancer*. 2017; 17: 358
- El Osta B, Behera M, Kim S, et al. Characteristics and outcomes of patients with metastatic KRAS-mutant lung adenocarcinomas: the lung cancer mutation consortium experience. *J Thorac Oncol* 2019;14:876-889
- Fong KM, Zimmerman PV, Smith PJ. KRAS codon 12 mutations in Australian non-small cell lung cancer. *Aust N Z J Med*. 1998;28:184-9
- Gao J, Wu H, Wang L, Zhang H, Duan H, Lu J, et al. Validation of targeted next-generation sequencing for RAS mutation detection in FFPE colorectal cancer tissues: comparison with sanger sequencing and ARMS-Scorpion real-time PCR. *BMJ Open*. 2016; 6: e009532
- Jeanson A, Tomasini P, Souquet-Bressand M, et al. Efficacy of immune checkpoint inhibitors in KRAS-mutant non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2019;14:1095-1101
- Lanman BA, Allen JR, Allen JG, et al. Discovery of a covalent inhibitor of KRAS<sup>G12C</sup> (AMG 510) for the treatment of solid tumors. *J Med Chem* 2020;63:52-65
- Lindeman NI, Cagle PT, Aisner DL, et al. 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. *J Thorac Oncol* 2018;13:323-358
- Mascaux C, Iannino N, Martin B, et al. The role of RAS oncogene in survival of patients with lung cancer: a systematic review of the literature with meta-analysis. *Br J Cancer* 2005; 92: 131-9
- Mitchell P, et al Lung cancer in Victoria: are we making progress? *MJA* 2013; 199: 674-9.
- Nadal E, Chen G, Prensner JR, et al. KRAS-G12C mutation is associated with poor outcome in surgically resected lung adenocarcinoma. *J Thorac Oncol* 2014; 9: 1513-22.

NPACC 2017. Requirements for human medical genome testing utilising massively parallel sequencing technologies. First edition 2017. D. of H.

NPACC 2013. Requirements for medical testing of human nuclei acids. Second edition 2013 D. of H.  
Pan W, Yang Y, Zhu H, et al. KRAS mutation is a weak, but valid predictor for poor prognosis and treatment outcomes in NSCLC: A meta-analysis of 41 studies. *Oncotarget* 2016;7:8373-8388

Rekhtman N, Paik PK, Arcila ME, et al. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous cell carcinoma of the lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. *Clin Cancer Res* 2012;18(4):1167-1176

Russell PA, Rogers T-M, Solomon B, et al. Correlation between molecular analysis, diagnosis according to the 2015 WHO classification of unresected lung tumours and TTF1 expression in small biopsies and cytology specimens from 344 non-small cell lung carcinoma patients. *Pathol* 2017;49: 604-610

Shepherd FA, Domerg C, Hainaut P, et al. Pooled analysis of the prognostic and predictive effects of KRAS mutation status and KRAS mutation subtype in early-stage resected non-small cell lung cancer in four trials of adjuvant therapy. *J Clin Oncol* 2013; 31: 2173-81

Sherwood JL, Brown H, Rettino A, et al. Key differences between 12 KRAS mutation detection technologies and their relevance for clinical practice. *ESMO Open* 2017;2:e000235.  
doi:10.1136/esmopen-2017-00235

Sherwood JL, Dearden S, Ratcliffe M, Walker J. 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. *J Exp Clin Cancer Res* 2015;34:92

Tan L, Alexander M, Officer A, et al. Survival difference according to mutation status in a prospective cohort study of Australian patients with metastatic non-small-cell lung carcinoma. *Int Med J* 2018; 48 :37-44

Tuononen K, Maki-Nevala S, Kaur Sarhadi V, et al. Comparison of targeted next-generation sequencing (NGS) and real-time PCR in the detection of EGFR, KRAS, and BRAF mutations on formalin-fixed paraffin-embedded tumor material of non-small cell lung carcinoma – superiority of NGS. *Genes, Chromosomes & Cancer* 2013;52:503-511