Australian Government

Department of Health

MSAC Application 1721

Small gene panel testing for non-small cell lung carcinoma (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
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: The Royal College of Pathologists of Australasia

ABN: 52 000 173 231

Business trading name: The Royal College of Pathologists of Australasia

Primary contact name: **REDACTED**

Alternative contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

Alternative contact name: **REDACTED**

Alternative contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

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

Small gene panel testing for non-small cell lung carcinoma (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)

In 2021 there were a total of 13,810 cases of lung cancer diagnosed in Australia, making it the fifth most common cancer with an age-standardised rate (ASR) of 42.6 cases per 100,000 persons.2 Although it is the fourth most common cancer in males and females alone, behind prostate/breast (respectively), colorectal and melanoma, it affects more males than females (ASR of 48.8 versus 37.4 per 100,000, respectively). Rates of mortality are high as most patients present with incurable advanced stage disease. There were an estimated 8,693 deaths from lung cancer in 2021, making it the leading cause of death by cancer in Australia in both men and women, with a slightly higher number of males than females effected (ASR of 32.7 versus 21.3, respectively).3

There are two broad classes of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which accounts for 85% of all lung cancers and is the focus of this application. The most common NSCLCs are:

- adenocarcinoma (approximately 40% of all lung cancers), which is most commonly diagnosed in current or former smokers, but is also the most common lung cancer in non-smokers;
- squamous cell carcinoma, which commonly develops in the larger airways of the lung and is strongly associated with smoking; and
- large cell undifferentiated carcinoma, which can affect any part of the lung and is a diagnosis of exclusion, being not clearly squamous cell or adenocarcinoma.[4, 5]

Most patients are symptomatic at the time of diagnosis and a biopsy or cytology specimen is obtained for diagnosis and treatment decision making in most cases. Depending on the stage of disease and the type of lung cancer, treatment options offered either alone or in combination may include surgery, radiotherapy, chemotherapy, immunotherapy, or molecularly targeted therapy.[6] In patients with advanced stage disease when surgical resection is no longer an option, molecular subtyping of non-small cell lung carcinomas is required to determine if a molecularly targeted therapy is indicated (such as an epidermal growth factor tyrosine kinase inhibitor), or if chemotherapy, immunotherapy or a combination is required.

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)

Molecular testing using a small gene panel approach can identify actionable genetic alterations responsive to currently available targeted therapies in a significant proportion of NSCLC patients. Tyrosine kinase inhibitors that target *EGFR, ALK* and *ROS1* genetic alterations in NSCLC are approved and reimbursed in Australia and tyrosine kinase inhibitors targeting *KRAS, BRAF V600E, MET* Exon 14, *RET* and *NTRK*[*] genetic alterations are approved in the USA[6] and being considered for approval and reimbursement in Australia.

The consolidation of multiple molecular biomarker tests into small next generation sequencing panels that test for multiple genetic alterations at once avoids the need to perform sequential single gene testing. Reducing the number of DNA/RNA extractions needed to be performed on a single biopsy reduces the risk of sample depletion and the need to perform an additional invasive biopsy procedure. In addition, this comprehensive approach results in improved patient outcomes obtained with a minimum turnaround time.

[*] *EGFR* = epidermal growth factor receptor, *ALK* = anaplastic lymphoma kinase, *KRAS* = Kirsten rat sarcoma and *NTRK* = neurotrophic tyrosine receptor kinase

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:

N/A

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

N/A

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

☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
☒ 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)
☐ A new item for a specific single consultation item
☐ 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:

N/A

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)*:

☐ To be used as a screening tool in asymptomatic populations
☒ Assists in establishing a diagnosis in symptomatic patients
☒ Provides information about prognosis
☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
☐ 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?

N/A

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

(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?

N/A

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

N/A

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

Pathology laboratories would use standard consumable items/reagents and equipment during the preparation of tissue specimens for next generation sequencing panel testing using DNA and RNA. This would include reagents for nucleic isolation, reverse transcription (for RNA panel), library preparation, enrichment, hybridisation and capture, enriched library amplification and amplified library clean-up and normalisation.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

The National Association of Testing Authorities (NATA) and the Royal College of Pathologists Australasia (RCPA) oversee the regulation of pathology testing for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189, and specifically accredited to provide genetic testing. This accreditation process covers the technical aspects of the sample reception and processing, laboratory sequencing, analysis pipelines, curation (or interpretation) of results and production of the report to a clinical standard. There are no requirements for use of specific manufacturer's reagents, equipment or analysis pipelines.

Note: A non-commercial IVD is required to be regulated but not to be listed on the ARTG: testing using an IVD would be delivered only by Approved Practising Pathologists in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral in line with other tests in the MBS Pathology Table.

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: N/A

Manufacturer's name: N/A

Sponsor's name: N/A

(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 **IVD**
☐ 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

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

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

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	Short description of research	Website link to journal article or research
Guidelines (2021)[7] USA	NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer	National Comprehensive Cancer Network (NCCN) recommends the following genomic alterations should be performed as part of the diagnostic work-up of NSCLC patients: *EGFR; ALK; ROS1; BRAF; KRAS*. The following emerging genomic alterations are also identified which may play a role in the management of NSCLC patients in the future: *MET; RET*; and *HER2*; All of these genomic alterations are assessed simultaneously using the same biopsy sample with NGS assays.	https://pubmed.ncbi.nlm.nih.gov/33668021/
Guidelines (2020)[8] Europe	Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group	Based on the current evidence, the European Society for Medical Oncology (ESMO) recommends routine use of NGS on tumour samples in advanced NSCLC in order to detect level I alterations (*EGFR, ALK, MET* ex 14 skipping, *BRAF, ROS1, NTRK, RET*). Considering the high frequency of fusions, RNA-based NGS, or DNA-based NGS designed to capture such fusions, are the preferred options.	https://pubmed.ncbi.nlm.nih.gov/32853681/
Guidelines (2018) [9] USA	Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors	The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology updated recommendations include testing of all advanced stage lung adenocarcinoma patients for EGFR, ALK and ROS1 alterations. Additional genes (*ERBB2, MET, BRAF, KRAS,* and *RET*) are recommended for laboratories that perform next-generation sequencing panels. The CAP/IASLC/AMP guidelines are currently being updated.	https://pubmed.ncbi.nlm.nih.gov/29355391/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Guidelines (2020) [10] Spain	Updated guidelines for predictive biomarker testing in advanced non-small-cell lung cancer: a National Consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology	The Spanish Society of Medical Oncology and the Spanish Society of Pathology updated guidelines on biomarker testing in patients with advanced non-small-cell lung cancer (NSCLC) based on current evidence. Current evidence suggests that the mandatory tests to conduct in all patients with advanced NSCLC are for EGFR and BRAF mutations, ALK and ROS1 rearrangements and PD-L1 expression. The growing need to study other emerging biomarkers has promoted the routine use of next-generation sequencing.	https://pubmed.ncbi.nlm.nih.gov/31598903/
Data set (2013)[11] Australia, UK, USA, Canada	Data Set for Reporting of Lung Carcinomas	Recommendations From International Collaboration on Cancer Reporting Evidence-based recommendations on immunohistochemical and molecular markers to aid in the typing of lung carcinoma. *Currently being updated	https://pubmed.ncbi.nlm.nih.gov/23899061/
Economic analysis (2020)[12] Canada	Comprehensive genomic profiling for non-small-cell lung cancer: health and budget impact	The model is defined by a reference scenario, in which only single conventional tests are used, and by an adoption scenario, where patients are simultaneously test for EGFR, ALK, ROS1, BRAF, MET, ERBB2, RET, and KRAS alterations and other alterations of interest. When simultaneous testing replaced single testing with 50% uptake, the budget impact per person per year ranged from C$0.71 to C$0.87, depending on the reference scenario, with a 3-year gain of 680.9 life–years and 3831 working days over the full cohort. Simultaneous testing could optimise the selection of appropriately targeted treatments, adding life–years and productivity with minimal budget impact.	https://pubmed.ncbi.nlm.nih.gov/33380872/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Economic analysis (2018)[13] USA	Budget Impact of Next-Generation Sequencing for Molecular Assessment of Advanced Non-Small Cell Lung Cancer	A Markov model was developed to evaluate the budget impact to a health plan payer of single-gene testing (*EGFR, ALK, ROS1, BRAF, MET, HER2*,and *RET*) versus NGS for non-squamous NSCLC used to guide first-line treatment in a hypothetical cohort of 1 million patients over 5-years. NGS, instead of single-gene testing, decreased expected testing procedure-related costs to the health plan payer by US$24,651. First-line and maintenance treatment costs increased by US$842,205, offset by a US$385,000 decrease in second-line treatment and palliative care costs. NGS is expected to identify more patients with activating mutations, thereby better enabling selection for targeted therapy with the budget impact to US payers expected to be minimally cost-additive.	https://pubmed.ncbi.nlm.nih.gov/30442274/
Retrospective comparative (2020)[14] Italy	Comparison of Sequential Testing and Next Generation Sequencing in advanced Lung Adenocarcinoma patients - A single centre experience	1,758 NSCLC patients, 1,221 of whom underwent sequential testing and 537 with NGS panel. The prevalence of *EGFR, ALK* and *KRAS* alterations was similar between the stepwise and NGS groups (16.5% vs 14.3%, 6.3% vs 6.3% and 36% vs 33.5%, respectively). *ROS-1* rearrangements prevalence was higher in stepwise group (4.7% vs 0.7%) as was *MET* amplification (11.2% vs 2.2%), *MET* mutations (9.0% vs 2.4%), *HER2* amplification (3.3% vs 1.9%) and mutations (9.8% vs 3.0%), and *BRAF* mutations (4.5% vs 5.6%). Among the NGS group other mutations were found in 141 patients (26.3%) and the presence of concurrent mutations in 131 (24.4%). The stepwise algorithm presented a relevant dropout rate that increased at each step, with 11.4%, 16.4% and 49.3% respectively for *ALK, ROS1* and other analysis. Sequential testing's expenditure was €1,375 per patient, vs €770 for NGS.	https://pubmed.ncbi.nlm.nih.gov/32932213/
Comparative, Level II diagnostic accuracy (2016)[15] China	Assessment of the clinical application of detecting EGFR, KRAS, PIK3CA and BRAF mutations in patients with non-small cell lung cancer using next-generation sequencing	A blinded comparison of a small NGS panel in 188 consecutive patients with NSCLC to qPCR assays with 188 samples to detect mutations in *EGFR, KRAS*, *PIK3CA* and *BRAF*. 79 patients (42%) were 'wild type' for targeted regions of the four genes by both NGS and qPCR, and 109 patients (58%) carried alterations identified either by NGS or PCR, including 99 patients (53%) with single mutation, and 10 patients (5%) with double mutations. Analysis showed 93.3% concordance of reportable variants mutually covered in both NGS and qPCR assays, with a clinical sensitivity of 89.9%, specificity of 97.5%, PPV of 97.8% and NPV of 88.6%. 89 mutations were identified by both NGS and qPCR, 10 were reported only by qPCR, and 20 only by NGS.	https://pubmed.ncbi.nlm.nih.gov/27215271/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Comparative, Level III-1 diagnostic accuracy (2018)[16] China	Next-generation sequencing-based detection of *EGFR, KRAS, BRAF, NRAS, PIK3CA*, *HER2* and *TP53* mutations in patients with non-small cell lung cancer	112 non-consecutive patients with NSCLC underwent small NGS panel testing (*BRAF, EGFR, KRAS, NRAS, PIK3CA, HER-2* and *TP53)* compared to qPCR with Sanger sequencing used to verify inconsistent results. *EGFR* variants were detected in 58/112 (51.79% of tumours), *KRAS* in 8.93%, *BRAF* in 1.79%, *NRAS* in 1.79%, *Her-2* in 1.79%, *PIK3CA* in 5.36% and *TP53* in 27.69%. There were 27 samples without a variant, 61 samples had a single variant whilst 24 samples had 2 or more variants. Compared to Sanger sequencing, the total sensitivity and specificity of NGS assays was 95.24% and 77.14%, respectively.	https://pubmed.ncbi.nlm.nih.gov/29956783/
Comparative, Level III-2 diagnostic accuracy (2022)[17] South Korea	Comparison of the Data of a Next-Generation Sequencing Panel from K-MASTER Project with That of Orthogonal Methods for Detecting Targetable Genetic Alterations	NGS results were compared to non-NGS orthogonal methods *EGFR*, *ALK* fusion, and *ROS1* fusion in 109 NSCLC patients. The sensitivity and specificity of NGS for *EGFR* were 86.2% and 97.5%, respectively. The concordance rate for *ALK* fusion was 100%, but ROS1 fusion was positive in only one of three cases that were positive in orthogonal tests.	https://www.e-crt.org/journal/view.php?doi=10.4143/crt.2021.218
Comparative, Level III-2 diagnostic accuracy (2019)[18] Portugal	Targeted Gene Next-Generation Sequencing Panel in Patients with Advanced Lung Adenocarcinoma: Paving the Way for Clinical Implementation	A Sanger sequencing plus FISH sequential approach for *EGFR* and *ALK* was compared to NGS in an experimental cohort of 117 patients with advanced lung adenocarcinoma. This was followed by an NGS-approach in an implementation cohort of 123 patients. Using Sanger and FISH, patients were classified as *EGFR*-mutated (n = 22, 18.8%), *ALK*-mutated (n = 9, 7.7%), and unclassifiable (UC) (n = 86, 73.5%). NGS identified at least one variant in 56 (47.9%) patients, totalling 68 variants among all samples. Combining NGS plus FISH for ALK, patients were classified as 23 (19.7%) *EGFR*; 20 (17.1%) *KRAS*; five (4.3%) *BRAF*; one (0.9%) *ERBB2*; one (0.9%) *STK11*; one (0.9%) *TP53*, and nine (7.7%) *ALK*.	https://pubmed.ncbi.nlm.nih.gov/31443496/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Comparative, Level III-2 diagnostic accuracy (2019)[19] China	Efficient ten-gene analysis of NSCLC tissue samples by next-generation sequencing	A 10-gene, 32-mutation detection NGS panel (*EGFR, KRAS, NRAS, PIK3CA, BRAF, HER2, MET, ALK, ROS1, RET*) was used to test 195 NSCLC samples. Sanger sequencing and PCR were used to verify *EGFR* and *ALK* results. Results: no mutations were found in 42 samples; 100 single and 5 *EGFR* double mutations were identified, *ALK* fusions (10%), *KRAS* mutations (6.5%), *HER2* mutations (2.5%), *RET* fusions (1.5%), *NRAS* and *PIK3CA* mutations (0.5%) were also found. Compared to using a few different technologies to analyse multigene mutations, a small NGS panel is a clinically applicable, efficient and affordable choice for NSCLC patients.	https://pubmed.ncbi.nlm.nih.gov/30876750/
Clinical utility (2021) [20] China	Utility of comprehensive genomic profiling in directing treatment and improving patient outcomes in advanced non-small cell lung cancer	1564 advanced NSCLC patients underwent NGS panel testing to identify potentially actionable genomic alterations. Tumour genomic profiles were established in 1,166 patients, leading to a matched targeted therapy in 37.7% (n = 440) and a genotype-matched trial enrolment in 20.9% of patients (n = 244). Potentially actionable alterations were detected in 781 patients (67.0%). For these patients, a genomic profiling-directed matched therapy significantly improved progression-free survival (9.0 months vs 4.9 months, $p < 0.001$) and overall survival (3.9 years vs 2.5 years, $p < 0.001$) compared with a non-matched therapy.	https://pubmed.ncbi.nlm.nih.gov/34592968/
Clinical utility (2021)[21] Austria	Reflex testing in non-small cell lung carcinoma using DNA- and RNA-based next-generation sequencing-a single-center experience	Retrospective comparison of NGS over 2 consecutive years (2019 and 2020). Comparing reflex testing with DNA-based NGS for mutations and immunohistochemistry (IHC) for *ALK, ROS1*, and *NTRK* fusion products, to DNA- and RNA-based NGS panels being simultaneously performed. Within the whole cohort (n=432), both DNA- and RNA-based NGS yielded almost always evaluable results. Only in 6 cases, the RNA content was too little for an appropriate analysis. After integrating RNA-based NGS in the reflex testing approach, the number of detected fusions increased significantly (2.6% vs. 8.2%; p=0.0021), but also more patients received targeted therapies. Furthermore, exceedingly rare alterations were more likely to be detected, including the so far undescribed *EGFR*-NUP160 fusion.	https://pubmed.ncbi.nlm.nih.gov/35004252/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Diagnostic yield and clinical utility (2021) Germany	Biomarker testing in non-small cell lung cancer in routine care: Analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315)[22]	3,717 patients with advanced NSCLC tested for *EGFR, ALK, ROS1, BRAF, KRAS, MET, TP53, RET, HER2*, as well as expression of *PD-L1*. The most common testing methods were IHC (68.5 % non-squamous, 58.3 % squamous), and NGS (38.7 % non-squamous, 14.4 % squamous). Reasons for not testing were insufficient tumour material or lack of guideline recommendations (squamous). No alteration was found in 37.8 % (non-squamous), and 57.9 % (squamous), respectively. Most common alterations in non-squamous tumours (all patients/all patients tested for the respective biomarker): *KRAS* (17.3 %/39.2 %), *TP53* (14.1 %/51.4 %), and *EGFR* (11.0 %/15.1 %); in squamous tumours: *TP53* (7.0 %/69.1 %), *MET* (1.5 %/11.1 %), and *EGFR* (1.1 %/4.4 %). Median PFS (non-squamous) was 8.7 months with druggable *EGFR* mutation, and 8.0 months with druggable *ALK* alterations.	https://pubmed.ncbi.nlm.nih.gov/33358484/

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	Short description of research	Website link to research	Date
Non-randomised interventional trial	Phase II Umbrella Study Directed by Next Generation Sequencing (TRUMP)	400 NSCLC patients assigned to 18 different treatment arms depending on their mutational status determined by NGS Outcomes: response time, progression free survival, overall survival	NCT03574402	Estimated Study Completion Date: December 30, 2024

Type of study design	Title of research	Short description of research	Website link to research	Date
Single arm intervention trial	Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity	This study is assessing the efficacy and safety of cabozantinib in patients with advanced NSCLC tumours harbouring genomic alteration in the following genes: RET; ROS1; or NTRK fusion, or increased MET or AXL activity. The duration of PFS and OS are secondary outcomes for this trial.	NCT01639508	Estimated Study Completion Date: July 2022
An observational cohort study	TOGA ASPiRATION study	An observational cohort study assessing the clinical impact of comprehensive genomic profiling in people with newly diagnosed metastatic lung cancer.	**ACTRN12616000908437**	Recruiting 1000 patients; due to complete recruitment Jan 2023

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 Medical Oncology Group of Australia (MOGA)
    - Thoracic Oncology Group of Australasia (TOGA)
    - Australian Genomics
    - Australian Pathology
    - Clinical Oncology Society of Australia (COSA)
    - Human Genetics Society of Australia
    - Australian & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS)

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

    N/A

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

    The Lung Foundation of Australia

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

    Manufacturers of commercially supplied NGS assays which may be used to test tumour tissue from NSCLC patients are:

    - Illumina: manufacturer of various solid tumour NGS panels, including the TruSight Oncology Panels (RUO assays)
    - ThermoFisher Scientific: manufacturer of various solid tumour NGS panels, including the Ion AmpliSeq Cancer Panels (RUO assays), oncomine precision assay
    - Roche Products (Roche Pharmaceuticals) are the owner of Foundation Medicine Inc who are the manufacturer of the FoundationOne® CDx assay (FDA-approved IVD companion diagnostic)
    - Roche Diagnostics: manufacturer of the AVENIO Tumor Tissue panels (RUO assays)

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**

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:

There are two broad classes of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which accounts for 85% of all lung cancers and is the focus of this application. The most common NSCLCs are:

- adenocarcinoma (approximately 40% of all lung cancers), which is most commonly diagnosed in current or former smokers, but is also the most common lung cancer in non-smokers;
- squamous cell carcinoma, which commonly develops in the larger airways of the lung and is strongly associated with smoking; and
- large cell undifferentiated carcinoma, which can affect any part of the lung and is a diagnosis of exclusion, being not clearly squamous cell or adenocarcinoma.[4, 5]

Most patients are symptomatic at the time of diagnosis and a biopsy or cytology specimen is obtained for diagnosis and treatment decision making in most cases. Depending on the stage of disease and the type of lung cancer, treatment options offered either alone or in combination may include surgery, radiotherapy, chemotherapy, immunotherapy, or molecularly targeted therapy.6 In patients with advanced stage disease when surgical resection is no longer an option, molecular subtyping of non-small cell lung carcinomas is required to determine if a molecularly targeted therapy is indicated (such as an epidermal growth factor tyrosine kinase inhibitor), or if chemotherapy, immunotherapy or a combination is required.

Due to the availability of targeted therapies specific for NSCLC patients, guidelines recommend the inclusion of *EGFR* (15% of NSCLC harbour EGFR exon 19 deletions or exon 21 L858R substitutions), *ALK* (5% of NSCLC have ALK rearrangements), *ROS1, BRAF, MET* ex 14 skipping, RET in a small NGS panel[7-9] as a minimum; however some guidelines also recommend the inclusion of *HER2*[7], *NTRK*[8], *KRAS*[7, 9] and *ERBB2*[9]. Treatment options with oral tyrosine kinase inhibitors (TKIs) depend on the identification of specific variants. In addition, access to most immunotherapeutic agents requires demonstration of absence of specific targetable gene mutations such as EGFR and ALK. Recommended targeted therapies approved for use in Australia by the PBAC are summarised in Table 1.

Table 1 Targeted therapies recommended for the treatment of NSCLC[23]

Variant(s)	Targeted therapies available on the PBS
EGFR	Gefitinib, erlotinib, afatinib, osimertinib
ALK	Crizotinib, ceritinib, alectinib, lorlatinib
ROS1	Crizotinib
BRAF V600E	Vemurafenib, dabrafenib + trametinib (all only approved for malignant melanoma)
RET	Cabozantinib (only approved for renal cell carcinoma)

Note that some therapies are listed by the PBS but for other indications. NSCLCs harbouring abnormalities in *EGFR* and treated with gefitinib, erlotinib, afatinib, and ALK/ROS1 treated with crizotinib have consistently led to more favourable outcomes compared with traditional chemotherapy. Variants leading to resistance to first-line EGFR and ALK TKIs can be inhibited by third-generation EGFR TKIs (osimertinib, rociletinib) and second-generation ALK TKIs (ceritinib, alectinib, lorlatinib). Other indications for TKIs include *ROS1* rearrangements (1-2% of tumours, drug: crizotinib), *BRAF*-V600E mutations (1-3% of tumours, drugs: vemurafenib, dafrafenib + trametinib), *MET* exon 14 skipping mutations (2-4% of tumours, drug: crizotinib); high-level *MET* amplification (1-2% of tumours,

drug: crizotinib); *RET* rearrangements (1% of tumours, drug: cabozantinib); and *ERBB2* mutations (2-3% of tumours, drug: afatinib).[23]

In 2021 there were a total of 13,810 cases of lung cancer diagnosed in Australia, making it overall the fifth most common cancer with an age-standardised rate (ASR) of 42.6 cases per 100,000 persons.[2] However, lung cancer is the fourth most common cancer in males and females, behind prostate/breast (respectively), colorectal and melanoma, affecting more males than females (ASR of 48.8 versus 37.4 per 100,000, respectively). Interestingly over the past 20 years, rates of lung cancer per person have remained relatively stable (ASR of 43.7 in 2001 vs 42.6 in 2021); however, rates have been decreasing steadily in males over time (ASR of 62.9 in 2001 vs 48.8 in 2021), whereas rates have been steadily increasing in females (ASR of 28.4 in 2001 vs 37.4 in 2021) (Figure 1). The difference in rates over time mirrors the changes in male and female smoking rates.[2, 3] however, in Western populations up to 20% of lung cancer patients have never smoked and the proportion of non-smokers is even higher in Asian populations.[24, 25]

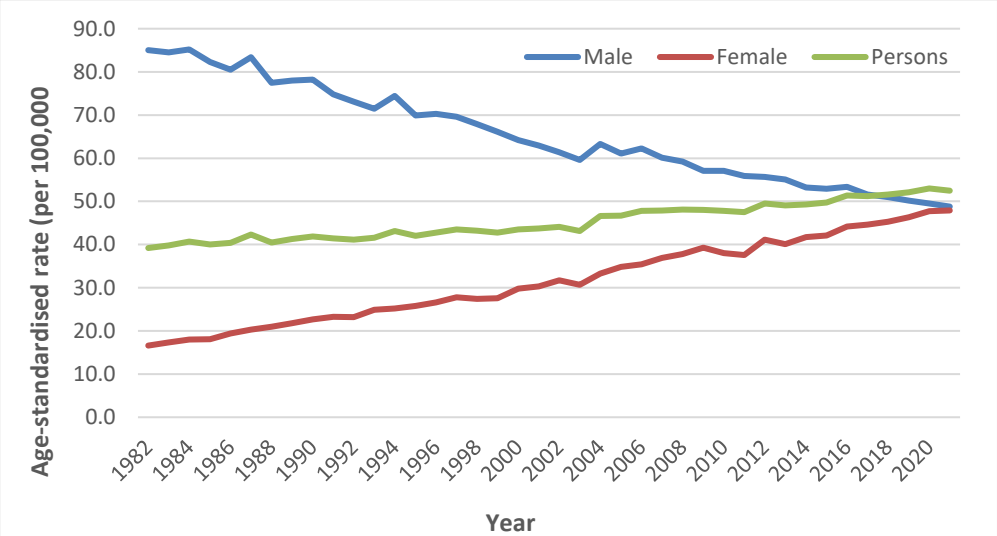

Figure 1 *Age-standardised incidence rates for lung cancer in Australia, 1982 to 2021, by sex*[1]

Patients with advanced lung cancer have a poor prognosis. The 5-year survival rates for patients with stage III NSCLC ranges from 36% (stage IIIA) to 13% (stage IIIC), and only 10% for those with stage IV. In 2021, there were 8,693 deaths from lung cancer, making it the most common cause of death by cancer, affecting a corresponding higher number of males than females (ASR of 32.7 versus 21.3, respectively).

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:

Patients diagnosed with non-squamous NSCLC (adenocarcinoma, large cell carcinoma or non-small cell carcinoma-not otherwise specified) on histopathological or cytological investigation of tumour material would be eligible for this service to determine suitability for available targeted therapies as per international guidelines and in line with current MBS item numbers for single gene testing for *EGFR, ALK* and *ROS1* alterations in lung cancer.

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 clinical management pathway (see Figure 2) would be identical to current NSCLC investigation and treatment:

- Patient presents to general or specialist medical practitioner with evidence or suspicion of lung cancer
- Patient is referred to a specialist for investigations that would include radiology and pathology
- Investigations would involve conducting histology/cytology specimens taken by biopsy or tumour resection, and a diagnosis is made without specific molecular testing
- If the diagnosis is a non-squamous NSCLC, the pathologist would initiate further pathological investigations on the biopsy material to identify genomic variants to determine appropriate therapy. Currently this would consist of sequential, single gene testing: *EGFR, ALK* and *ROS1*.

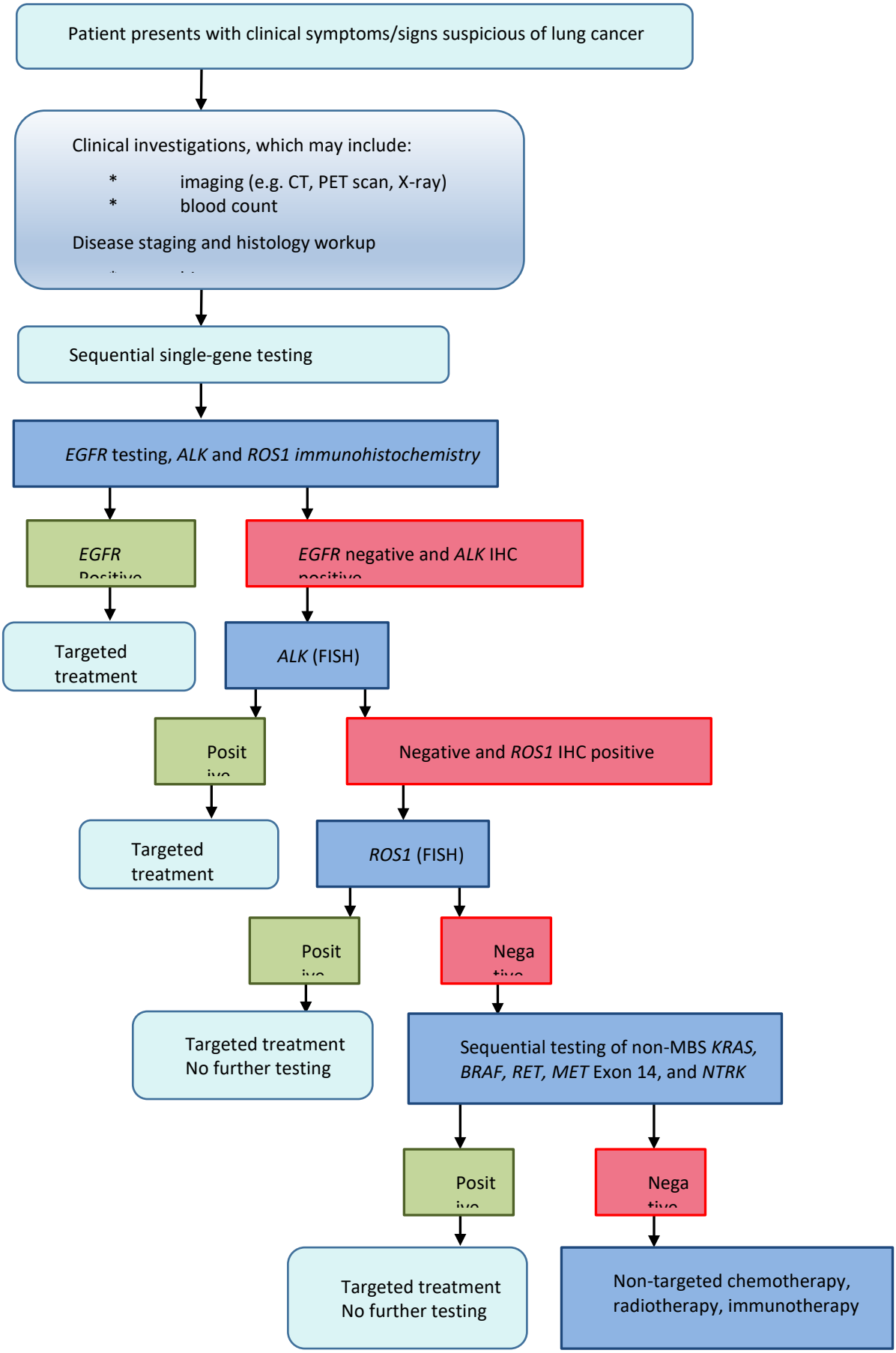

Figure 2 *Current clinical management algorithm showing sequential molecular biomarker testing strategy*

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

See Q25. Patients will undergo the same steps in evaluation; however, instead of single gene testing, panel testing will be conducted on biopsied tumour samples. NGS panel testing involves nucleic acid extraction from biopsy sample, which then undergoes target enrichment using either hybridisation-based target enrichment or amplicon-based target enrichment. The most widely used molecular characterisation technique for clinical applications is targeted panels that focus on a certain number of genes or gene regions. The sequence data is processed by a bioinformatics pipeline which includes sequence read alignment and variant calling and annotation. Genomic variants are then curated by scientists/pathologists and a clinical report generated.

Testing occurs in a NATA accredited diagnostic laboratory in accordance with NPAAC guidelines - Requirements for human medical genome testing utilising massively parallel sequencing technologies.

The results of these genomic tests are then interpreted with the rest of the pathological data of the patient to categorise the patient.

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

N/A

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?

N/A

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):

Testing should be pathologist determinable in order to provide definitive diagnosis/classification.

Once off diagnostic test per episode of disease.

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

Nil

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

Testing would be requested by the treating clinician and provided by Approved Practising Pathologists in line with other tests on the MBS Pathology Table.

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

N/A

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

Patients should be referred by a respiratory specialist/oncologist or consultant physician.

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 would be delivered only by Approved Practising Pathologists with appropriate scope of practice in NATA 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.

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:

N/A

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):

The appropriate comparator is the use of sequential, single variant testing currently listed on the MBS:

- testing of *EGFR* gene mutation status;
- immunohistochemistry testing as triage for *ALK* testing;
- testing of *ALK* gene rearrangement status by FISH;
- immunohistochemistry testing as triage for *ROS1* testing;
- testing of *ROS1* gene rearrangement status by FISH;

If a NSCLC patient tests positive for an *EGFR* mutation they are highly unlikely to have another targetable 'driver' mutation such as an *ALK* or *ROS1* rearrangement. Detecting an *EGFR* mutation would avoid testing for, *ALK* or *ROS1* mutations. It should be noted; however, that panel testing would pick up those rare patients with more than one variant.

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 number 73337:

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

- if the requirements relating to *epidermal growth factor receptor (EGFR)* gene status for access to an EGFR tyrosine kinase inhibitor under the Pharmaceutical Benefits Scheme are fulfilled; or

- if the requirements relating to *EGFR* status for access to pembrolizumab under the Pharmaceutical Benefits Scheme are fulfilled.

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

MBS item number 72846: Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 antibodies except those listed in 72848

Fee: $59.60 Benefit: 75% = $44.70 85% = $50.70

MBS item number 73341: Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (ALK) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score > 0, and with documented absence of activating mutations of the epidermal growth factor receptor (EGFR) gene, requested by a specialist or consultant physician, to determine:

- if requirements relating to *ALK* gene rearrangement status for access to an anaplastic lymphoma kinase inhibitor under the Pharmaceutical Benefits Scheme are fulfilled; or
- if requirements relating to *ALK* status for access to pembrolizumab under the Pharmaceutical Benefits Scheme are fulfilled.

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

MBS item number 73344: Fluorescence in situ hybridization (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small-cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of ROS proto-oncogene 1 (ROS1) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+; and with documented absence of both activating mutations of the *epidermal growth factor receptor (EGFR*) gene and anaplastic lymphoma kinase (ALK) immunoreactivity by IHC, requested by a specialist or consultant physician, to determine:

- if requirements relating to *ROS1* gene arrangement status for access to crizotinib or entrectinib under the Pharmaceutical Benefits Scheme are fulfilled; or
- if requirements relating to ROS1 status for access to pembrolizumab under the Pharmaceutical Benefits Scheme are fulfilled.

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

Note that *RAS* mutation testing is listed on the MBS (item number 73338) for testing in patients with colorectal cancer, and that *BRAF* V600 testing is listed (item number 73336) for patients with melanoma. In addition, it should be noted that in November 2020 the MSAC did not support public funding for *NTRK* fusion testing (MSAC application 1602) in patients with locally advanced or metastatic solid tumours due to the PBAC deferring its decision regarding larotrectinib, the co-dependent targeted medicine.

MBS item number 73351: A test of tumour tissue that is derived from a new sample from a patient with locally advanced (Stage IIIb) or metastatic (Stage IV) non-small cell lung cancer (NSCLC), who has progressed on or after treatment with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI). The test is to be requested by a specialist or consultant physician, to determine if the requirements relating to *EGFR* T790M gene status for access to osimertinib under the Pharmaceutical Benefits Scheme are fulfilled.

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

Note: This item would not be replaced and would stand alone as a repeat test if patients experience disease progression on an *EGFR* TKI

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):

Several tyrosine kinase inhibitors are currently listed on the PBS for use in NSCLC patients who test positive for specific variants. It should be noted that there are currently several TKIs in the development pipeline that may come online in the near future

Table 2 Targeted therapies recommended for the treatment of NSCLC[6]

Variant(s)	Targeted therapies available on the PBS
EGFR (10%–30% of NSCLC tumours)	Gefitinib, erlotinib, afatinib, osimertinib
ALK (5% of NSCLC tumours)	Crizotinib, ceritinib, alectinib, brigatinib
	Crizotinib
ROS1 (1%–2% of NSCLC tumours)	Ceritinib, entrectinib, lorlatinib recommended
NTRK (*~0.*2% of NSCLC tumours)	Entrectinib, larotrectinib recommended
MET exon 14 skipping (2-4% NSCLC)	Cabozantinib (only approved for renal cell carcinoma)
BRAF V600E (1–3% of NSCLC tumours)	Vemurafenib, dabrafenib + trametinib (all only approved for malignant melanoma)
RET (1%–2% of NSCLC tumours)	Cabozantinib (only approved for renal cell carcinoma)

Patients who test negative for all variants listed on the MBS (*EGFR, ALK, ROS1*), have the option to pay for further molecular testing (e.g. *KRAS, RET, BRAF V600E, MET* exon 14, and *NTRK*) on an out-of-pocket basis. Some State-based services may also pay for further testing.

For those patients who test negative for all biomarkers, treatment options may include chemotherapy, immunotherapy, radiation therapy, or a combination of modalities. For early-stage NSCLC, surgical resection is the treatment of choice. Patients with stage I or II NSCLC would undergo resection and if found to be pathologic stage IB or stage II/III, they may then undergo adjuvant chemotherapy. Patients with positive margins require postoperative radiation therapy or reresection followed by adjuvant chemotherapy. Programmed cell death ligand 1 (PD-L1) expression should be quantified in patients lacking a driver mutation. If PD-L1 levels are greater than 50 percent, then immunotherapies directed against the PD-1 receptor on the cell surface such as pembrolizumab or atezolizumab (both listed on the PBS for NSCLC) may be administered, with or without chemotherapy.[4]

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)

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

Although it is expected that small panel testing in NSCLC patients will become standard clinical practice over time, many Australian laboratories currently will not have the capability to run panels and will still require access to existing single gene testing MBS item numbers, at least initially until NGS testing can be established. Also some tumours may not be suitable for NGS testing and will need a single gene/FISH based approach, although the number should be low _5-10% cases.

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):

Small panel testing is an alternative to sequential, single gene tests that are currently listed on the MBS and used to determine eligibility for NSCLC patients to access specific PBS-listed targeted treatments. Small panel testing will not result in any change to the clinical management pathway for NSCLC patients, however, a significantly shorter testing turnaround time will result in faster access to appropriate treatment for patients, which may translate to overall better patient outcomes.

There are two potential approaches to small panel testing, the use of which may depend on each individual laboratory's capacities and infrastructure:

1. one MBS item number describing a "nucleic acid" panel, combining both DNA/RNA. A combined panel would be less widely available (currently) than option 2 and would involve testing for *ALK/ROS/RET/NTRK* fusions in patients that harbour other targetable mutations (eg *EGFR/KRAS/BRAF*) but would be faster overall and potentially have better patient outcomes than comparative sequential testing (Figure 3); or
2. Based on the differences in techniques to identify point mutations/small indels (as occur in *EGFR, KRAS, BRAF, MET*) from translocations resulting in fusion genes (eg *ALK, ROS1, RET*, *NTRK*), we propose two separate MBS item numbers for NGS panels with the first targeting *EGFR, KRAS, BRAF* and *MET* exon 14 skipping mutations (DNA panel), covering the most common alterations, and if this is negative, a 2nd fusion (RNA) panel covering *ALK, ROS1, RET* and *NTRK* (Figure 4).

As there are advantages and disadvantages with both approaches, the College would welcome a discussion with the Department as to whether it is feasible to list both, or just the one approach.

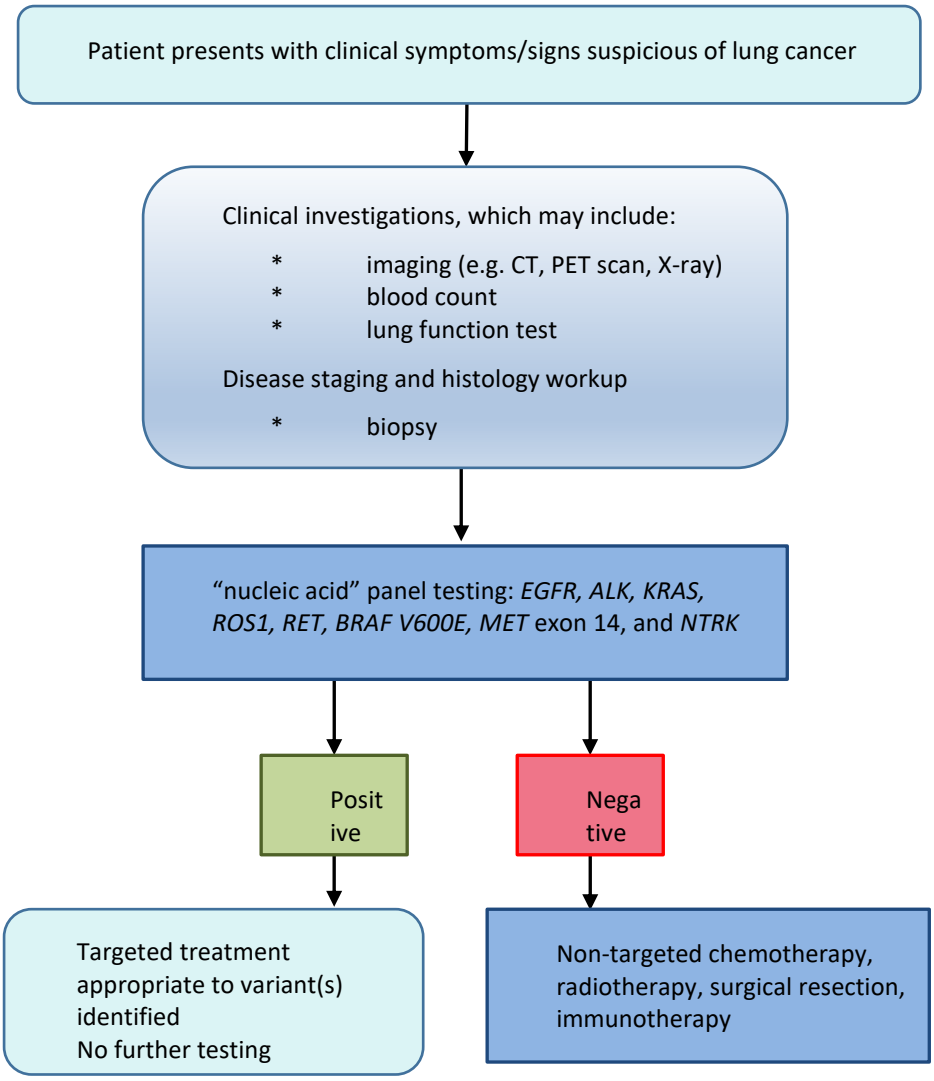

Figure 3 Proposed clinical management algorithm using a combined "nucleic acid" small panel test

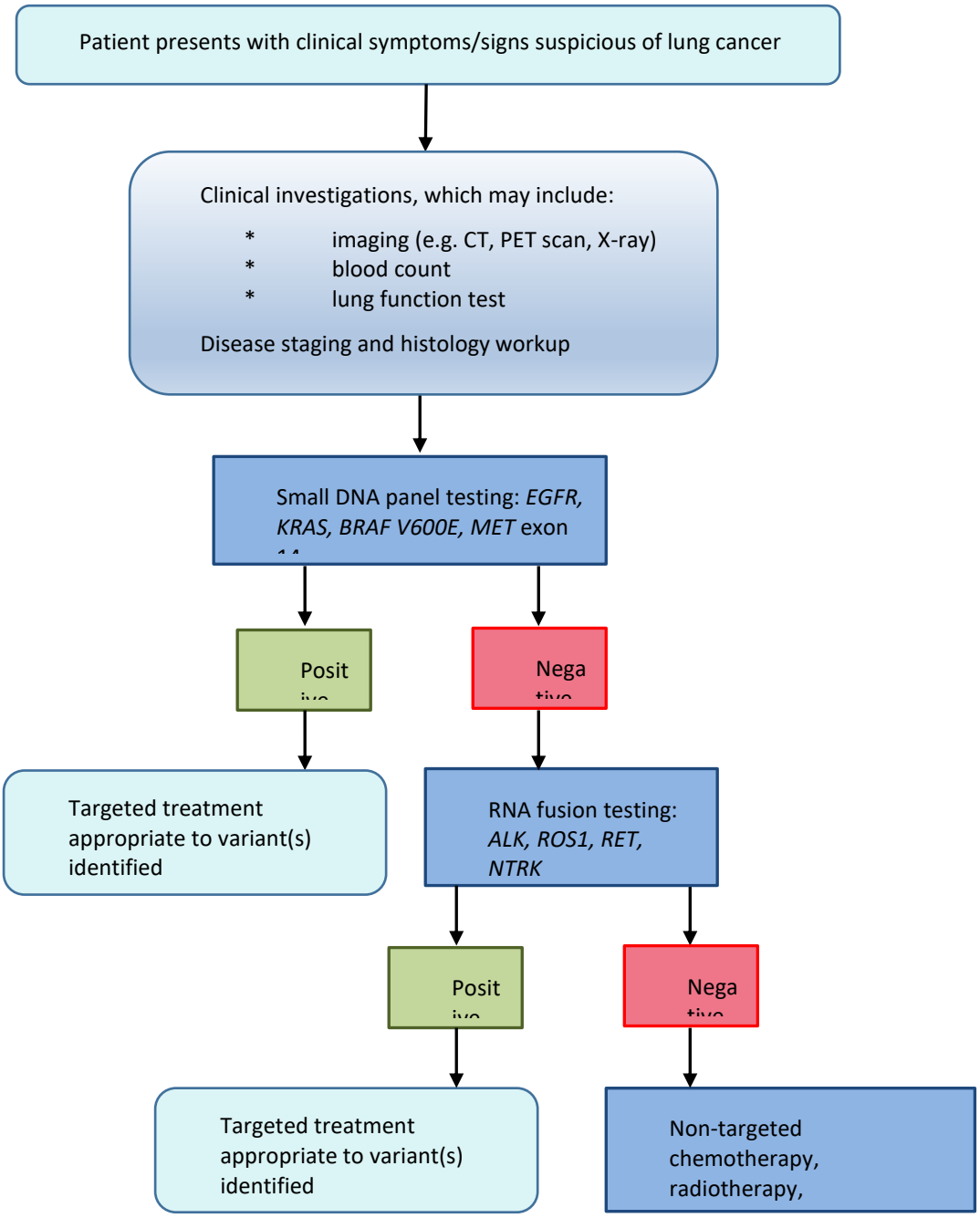

Figure 4 *Proposed clinical management algorithm using a two panel, DNA and RNA approach*

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):

Sequential single variant testing (the comparator) is associated with the risk of running out of enough sample to conduct multiple analyses on, and as such may result in the patient needing to undergo a repeat biopsy. A small NGS panel should result in reduced re-biopsy rates. Depending on the type of variant identified, an NGS panel will have a more rapid turnaround time. Dall'Olio et al (2020) recently reported that, on average, a small NGS panel took 10 days for assessment and reporting results, compared to 13.5 days for sequential testing (noting that 10-30% of NSCLC have an EGFR variant which would be identified at step one in a sequential testing scenario). A faster turnaround time will translate to quicker access to appropriate treatment for patients. In addition, Dall'Olio reported markedly reduced overall costs per patient when using NGS compared to sequential testing (€770 versus €1,375, respectively[†]). Importantly, small panel testing can identify concurrent mutations at the same time. Although sequential testing could detect multiple variants, usually testing is halted once one variant is identified.[14]

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:

Safety Outcomes:

Test adverse events

Test failure and need to re-biopsy (rate of re-biopsy and harms from re-biopsy)

Adverse events from treatment

Adverse events from change in patient management

Clinical Effectiveness Outcomes:

Direct evidence:

Change in patient health outcomes: mortality, morbidity, quality of life

Indirect evidence

Health outcome changes as a result of change in management/treatment (an increase in number of patients eligible for PBS-listed targeted therapies and/or earlier commencement of treatment) resulting in change in patient outcomes: mortality, morbidity, quality of life

Health system resources:

Cost of gene panel

Cost of targeted therapies

Cost per quality-adjusted life year

Total Australian Government healthcare costs

[†] Equates to $1,233 versus $2,202 as of 8th February 2022

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

In 2021 there were a total of 13,810 cases of lung cancer diagnosed in Australia, making it the fifth most common cancer with an age-standardised rate (ASR) of 42.6 cases per 100,000 persons.[2] NSCLCs represent 85% of all lung cancers, which would equate to approximately 11,738 diagnosed in Australia in 2021. Although it is, the fourth most common cancer in males and females, behind prostate/breast, colorectal and melanoma, it affects more males than females (ASR of 48.8 versus 37.4 per 100,000, respectively). In 2021, there were 8,693 deaths from lung cancer, making it the most common cause of death by cancer, affecting a corresponding higher number of males than females (ASR of 32.7 versus 21.3, respectively). Over the past 20-30 years, rates of lung cancer per person have remained relatively stable in Australia.[2]

Over time, the mean age of diagnosis of lung cancer in Australia has been steadily increasing and was 71.2 years in 2017 (Figure 5).[2]

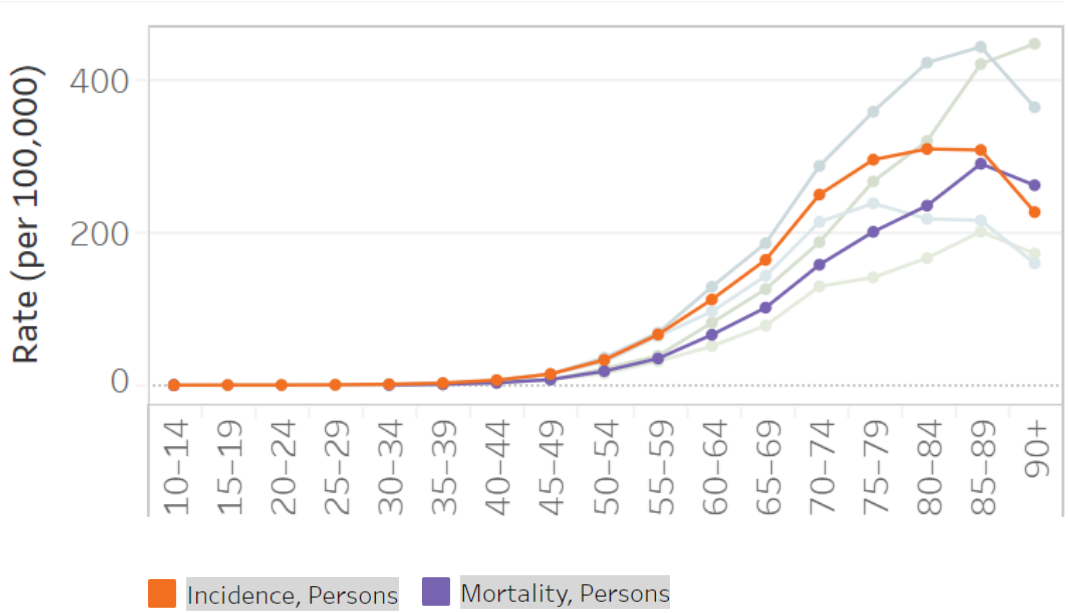

Figure 5 *The incidence and rate of mortality of lung cancer in Australia by age*[2]

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

Once off diagnostic test per episode of disease.

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

Once off diagnostic test per episode of disease.

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

NSCLC represents 85% of all lung cancers, but only non-squamous non-small cell lung carcinomas require multigene testing therefore not all incident cases of lung cancer would require small panel testing. As *EGFR* testing is listed on the MBS and is the initial test used in a sequential testing strategy, the 4,924 *EGFR* tests (MBS item 73337) conducted in the 2020-2021 financial year is a reasonable indication of demand for small panel NGS 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:

The increase in *EGFR* item number usage from 2018-19 to 2019-20 was calculated to be 6.2 percent, and from 2019-20 to 2020-21 was 6.05%. Therefore, it is reasonable to expect that testing numbers will increase yearly by approximately 6.125% (Table 3).

Table 3 The number of MBS claims for EGFR testing (item number 73337) and projected testing numbers

	2018-19	**2019-20**	**2020-21**	**Projected 2022**	**Projected 2023**	**Projected 2024**
EGFR testing	4,371	4,643	4,924	5,226	5,546	5,886
% increase on previous year		6.2%	6.05%	6.125%	6.125%	6.125%

PART 8 – COST INFORMATION

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

Estimated fees are based on those currently in use for private patients, and reflects costs to deliver the tests, including extraction, pathologist assessment, QC, losses, curation, and reporting.

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

Turnaround time for small panel testing is approximately 10 days between sample receipt and reporting of all results.[9, 14]

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.

Proposed item number for Option 1:

Category 6 –Genetics P7

A nucleic acid-based multi-gene panel test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to detect:

i. variants in at least *EGFR*, *BRAF, KRAS* and *MET* exon 14 to determine access to specific therapies listed on the Pharmaceutical Benefits Scheme (PBS); and
ii. the fusion status of at least *ALK, ROS1, RET*, and *NTRK* to determine access to specific therapies listed on the PBS; or
iii. if the requirements relating to *EGFR, ALK* and *ROS1* status for access to pembrolizumab under the PBS are fulfilled.

Maximum one test per episode of disease

This item cannot be claimed in addition to MBS items 73337

Fee: $1,247 **Benefit:** 75% = $935.25 85% = $1,059.95

Proposed item numbers for Option 2: the 2-step "nucleic acid" panel. Item BBBB can only be claimed if item AAAA is negative.

AAAA Category 6 –Genetics P7

A DNA-based multi-gene panel test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to detect:

i. variants in at least *EGFR*, *BRAF, KRAS* and *MET* exon 14 to determine access to specific therapies listed on the Pharmaceutical Benefits Scheme (PBS); or
ii. if the requirements relating to *EGFR* status for access to pembrolizumab under the PBS are fulfilled.

Maximum one test per episode of disease

This item cannot be claimed in addition to MBS items 73337

Fee: $682.35 **Benefit:** 75% = $511.76 85% = $580

BBBB Category 6 –Genetics P7

A nucleic acid-based multi-gene panel test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, and with documented absence of activating mutations of the *EGFR* gene, K*RAS, BRAF* and *MET* exon14, requested by, or on behalf of, a specialist or consultant physician, to detect:

i. the fusion status of at least *ALK, ROS1, RET*, and *NTRK* to determine access to specific therapies listed on the Pharmaceutical Benefits Scheme (PBS) are fulfilled; or
ii. if the requirements relating to *ALK* and *ROS1* status for access to pembrolizumab under the PBS are fulfilled.

Maximum one test per episode of disease

This item can only be claimed if item number AAAA is negative, and cannot be claimed in addition to MBS items 73341, 73344

Fee: $682.35 **Benefit:** 75% = $511.76 85% = $580

REFERENCES

1. Cancer Data in Australia 2021: Book 1a – Cancer incidence (age-standardised rates and 5-year age groups) [database on the Internet]. Australian Institute of Health and Welfare. 2021 [Accessed 7th February 2022]. Available from: https://www.aihw.gov.au/getmedia/e8779760-1b3c-4c2e-a6c2-b0a8d764c66b/AIHW-CAN-122-CDiA-2021-Book-1a-Cancer-incidence-age-standardised-rates-5-year-age-groups.xlsx.aspx.

2. Cancer summary data visualisation [database on the Internet]. Australian Institute of Health and Welfare. 2021 [Accessed 31st January 2022]. Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation.

3. AIHW (2021). *Cancer in Australia 2021*, Australian Institute of Health and Welfare, Canberra https://www.aihw.gov.au/getmedia/0ea708eb-dd6e-4499-9080-1cc7b5990e64/aihw-can-144.pdf.aspx?inline=true.

4. Clark, S. B.& Alsubait, S. Non Small Cell Lung Cancer. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562307/.

5. Cancer Council Australia (2020). *Lung Cancer*. Available from: https://www.cancer.org.au/cancer-information/types-of-cancer/lung-cancer [Accessed 31st January 2022].

6. Alexander, M., Kim, S. Y.& Cheng, H. (2020). 'Update 2020: Management of Non-Small Cell Lung Cancer'. *Lung*, 198 (6), 897-907.

7. Ettinger, D. S., Wood, D. E. et al (2021). 'NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021'. *J Natl Compr Canc Netw*, 19 (3), 254-66.

8. Mosele, F., Remon, J. et al (2020). 'Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group'. *Ann Oncol*, 31 (11), 1491-505.

9. Lindeman, N. I., Cagle, P. T. et al (2018). 'Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology'. *Arch Pathol Lab Med*, 142 (3), 321-46.

10. Garrido, P., Conde, E. et al (2020). 'Updated guidelines for predictive biomarker testing in advanced non-small-cell lung cancer: a National Consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology'. *Clin Transl Oncol*, 22 (7), 989-1003.

11. Jones, K. D., Churg, A. et al (2013). 'Data set for reporting of lung carcinomas: recommendations from International Collaboration on Cancer Reporting'. *Arch Pathol Lab Med*, 137 (8), 1054-62.

12. Johnston, K. M., Sheffield, B. S. et al (2020). 'Comprehensive genomic profiling for non-small-cell lung cancer: health and budget impact'. *Curr Oncol*, 27 (6), e569-e77.

13. Yu, T. M., Morrison, C. et al (2018). 'Budget Impact of Next-Generation Sequencing for Molecular Assessment of Advanced Non-Small Cell Lung Cancer'. *Value Health*, 21 (11), 1278-85.

14. Dall'Olio, F. G., Conci, N. et al (2020). 'Comparison of Sequential Testing and Next Generation Sequencing in advanced Lung Adenocarcinoma patients - A single centre experience'. *Lung Cancer*, 149, 5-9.

15. Xu, X., Yang, Y. et al (2016). 'Assessment of the clinical application of detecting EGFR, KRAS, PIK3CA and BRAF mutations in patients with non-small cell lung cancer using next-generation sequencing'. *Scand J Clin Lab Invest*, 76 (5), 386-92.

16. Jing, C., Mao, X. et al (2018). 'Next-generation sequencing-based detection of EGFR, KRAS, BRAF, NRAS, PIK3CA, Her-2 and TP53 mutations in patients with non-small cell lung cancer'. *Mol Med Rep*, 18 (2), 2191-7.

17. Choi, Y. J., Choi, J. Y. et al (2022). 'Comparison of the Data of a Next-Generation Sequencing Panel from K-MASTER Project with That of Orthogonal Methods for Detecting Targetable Genetic Alterations'. *Cancer Res Treat*, 54 (1), 30-9.

18. Fernandes, M. G. O., Jacob, M. et al (2019). 'Targeted Gene Next-Generation Sequencing Panel in Patients with Advanced Lung Adenocarcinoma: Paving the Way for Clinical Implementation'. *Cancers (Basel)*, 11 (9).

19. Ji, X., Che, N. et al (2019). 'Efficient ten-gene analysis of NSCLC tissue samples by next-generation sequencing'. *Pathol Res Pract*, 215 (5), 1066-70.

20. Zhao, S., Zhang, Z. et al (2021). 'Utility of comprehensive genomic profiling in directing treatment and improving patient outcomes in advanced non-small cell lung cancer'. *BMC Med*, 19 (1), 223.

21. Zacharias, M., Absenger, G. et al (2021). 'Reflex testing in non-small cell lung carcinoma using DNA- and RNA-based next-generation sequencing-a single-center experience'. *Transl Lung Cancer Res*, 10 (11), 4221-34.

22. Griesinger, F., Eberhardt, W. et al (2021). 'Biomarker testing in non-small cell lung cancer in routine care: Analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315)'. *Lung Cancer*, 152, 174-84.

23. Shea, M., Costa, D. B.& Rangachari, D. (2016). 'Management of advanced non-small cell lung cancers with known mutations or rearrangements: latest evidence and treatment approaches'. *Ther Adv Respir Dis*, 10 (2), 113-29.

24. Wakelee, H. A., Chang, E. T. et al (2007). 'Lung cancer incidence in never smokers'. *J Clin Oncol*, 25 (5), 472-8.

25. Sun, S., Schiller, J. H.& Gazdar, A. F. (2007). 'Lung cancer in never smokers--a different disease'. *Nat Rev Cancer*, 7 (10), 778-90.