



**Australian Government**

**Department of Health**

# **MSAC Application 1660**

## **Diagnostic testing for mesenchymal-epithelial transition (MET) Exon 14 (METex14) skipping alterations in non-small cell lung cancer (NSCLC) to determine Pharmaceutical Benefits Scheme eligibility for tepotinib treatment**

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 name: Merck Healthcare Pty Ltd  
ABN: 72 006 900 830  
Business trading name: Merck Healthcare Pty Ltd

### Primary contact name: REDACTED

Primary 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

Not applicable

## PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

### 3. Application title

Diagnostic testing for MET Exon 14 (METex14) skipping alterations in non-small cell lung cancer (NSCLC) to determine PBS eligibility for tepotinib treatment

### 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)

NSCLC comprises approximately 85%-90% of all lung cancer. At the time of diagnosis, most patients present with advanced disease, making surgical resection unfeasible.

For the selection of therapies for advanced NSCLC, current clinical guidelines recommend performing molecular testing prior to the initiation of an anticancer drug (Ettinger et al., 2016; Kalemkerian et al., 2018; Planchard et al., 2018; Schrock et al., 2016). If a predictive oncogenic marker is identified, treatment with respective approved targeted agents is to be applied when possible (Ettinger et al., 2016).

The MET receptor plays an important role in embryogenesis, tumour growth and metastasis (Vuong et al., 2018). Genetic mutations that affect the splice sites of exon 14 of MET (METex14) were identified predominantly in NSCLC. The consequence of METex14 mutations is the expression of a truncated MET receptor with increased and sustained activation and impaired ubiquitin-mediated degradation, resulting in oncogenic activation of MET (Cortot et al., 2017). METex14 skipping alterations are reported to occur approximately in 3-5% of NSCLC (Awad et al., 2019; Sabari & Paik, 2017; Schrock et al., 2016; Tong et al., 2016).

### 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 the testing of tumour material in patients with NSCLC to detect METex14 skipping alterations, to determine eligibility for treatment with TEPMETKO® (tepotinib) through the PBS.

PBS subsidy will also be sought for TEPMETKO® (tepotinib) for the treatment of patients with advanced NSCLC and confirmed MET Exon 14 skipping alterations.

### 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:

Not applicable

### (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 TEPMETKO (tepotinib) 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

An integrated co-dependent (Category 1 from January 1, 2021) is proposed.

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

Trade name: TEPMETKO®

Generic name: Tepotinib

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

Not applicable

**(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)?**

Not applicable

**(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?**

Other companies may be developing similar tests but the detail is unknown.

**(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?**

Single or multi-use consumables for in-house developed in-vitro diagnostic (assays would be kits which may be used for DNA/RNA extraction or any kit for PCR or NGS methods). Details of consumables will be confirmed with relevant pathology laboratories and presented in the full submission dossier.

## 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: TEPMETKO® (tepotinib as hydrochloride monohydrate)

Manufacturer's name: Merck Healthcare KGaA

Sponsor's name: Merck Healthcare Pty Ltd

Type of therapeutic good: In-vitro diagnostic test

Manufacturer's name: **Test agnostic**. METex14 skipping alterations can be detected using commercially available platforms such as, but is not limited to, the OncoPrint® Focus Assay (Thermo Fisher). However it is expected that laboratories will develop in-house tests, accredited through NATA, and quality controlled through a Quality Assurance Program.

Sponsor's name: Various

- (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

TGA approved indication(s), if applicable: Class III in-house IVDs are listed with TGA for testing if a laboratory is accredited to perform the testing.

TGA approved purpose(s), if applicable: Molecular genetics - Genetic testing for chimerism and mosaic gene variants (cancer and somatic mosaicism) - Targeted panels for non-inherited (somatic) DNA/RNA changes.

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

Date of submission to TGA (pharmaceutical product): **REDACTED**

Estimated date by which TGA approval can be expected: **REDACTED**

TGA Application ID: **REDACTED**

TGA approved purpose(s), if applicable: **REDACTED**

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?

Not applicable

## 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***
<b>PHASE II trials</b>					
1	Phase II, single arm study	Tepotinib in non-small cell lung cancer with MET Exon 14 skipping mutations	Assessed efficacy/safety of tepotinib in advanced/metastatic NSCLC with confirmed METex14 skipping mutation. Data presented on 152 patients. Primary endpoint was objective response among 99 follow-up patients (for at least 9 months). Response analysed according to whether METex14 was detected using tissue (NGS; Oncomine Focus Assay) or liquid biopsy (NGS; Guardant360).	<a href="https://www.nejm.org/doi/full/10.1056/NEJMoa2004407">https://www.nejm.org/doi/full/10.1056/NEJMoa2004407</a>  and Supplement to: Paik PK, Felip E, Veillon R, et al. Tepotinib in non–small-cell lung cancer with MET Exon 14 skipping mutations. N Engl J Med 2020;383:931-43. DOI: 10.1056/NEJMoa2004407	3 September 2020
<b>DIAGNOSTIC STUDIES</b>					
2	Comprehensive genomic profiling	Characterisation of 298 patients with lung cancer harbouring MET Exon 14 skipping alterations	Comprehensive genomic profiling of 11,205 lung cancer specimens which reported an overall frequency of 2.7% of METex14 alterations in NSCLC patients	<a href="https://pubmed.ncbi.nlm.nih.gov/27343443/">https://pubmed.ncbi.nlm.nih.gov/27343443/</a>	September 2016

	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***
3	Comprehensive genomic profiling	Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and congers clinical sensitivity to MET inhibitors	Comprehensive genomic profiling from 38.028 patients to identify 221 cases with METex14 mutations. METex14 mutations are detected most frequently in lung adenocarcinoma (3%).	<a href="https://pubmed.ncbi.nlm.nih.gov/25971938/">https://pubmed.ncbi.nlm.nih.gov/25971938/</a>	August 2015
4	Genomic profiling study	MET Exon 14 mutations in non-small cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-met overexpression	The article reports NGS results from 6,376 cancers to identify those harbouring METex14 mutations.	<a href="https://pubmed.ncbi.nlm.nih.gov/26729443/">https://pubmed.ncbi.nlm.nih.gov/26729443/</a>	March 2016
<b>CLINICAL VALIDATION STUDIES</b>					
5	Clinical Validation study	Validation of the OncoPrint panel for next-generation sequencing of clinical tumour samples	The validation of the OncoPrint Focus fusion panels for clinical application in solid tumour testing of FFPE tissue.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6182325/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6182325/</a>	August 2018
6	Clinical application and validation study	Single centre experience with a targeted next generation sequencing assay for assessment of relevant somatic alterations in solid tumours	Clinical application and validation study of OncoPrint Focus Assay (NGS) using two independent patient cohorts to define the workflow, turnaround times, feasibility and reliability of OFA	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5293722/pdf/main.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5293722/pdf/main.pdf</a>	March 2017



OTHER STUDIES					
7	A systematic review and meta-analysis	Clinicopathological implications of MET Exon 14 mutations in non-small cell lung cancer – A systematic review and meta-analysis	A systematic review and meta-analysis of METex14 skipping alterations in NSCLC. From 168 studies, the author included 12 studies comprising of 18,464 NSCLCs for final analysis. Prevalence of METex14 in NSCLC was 3% and was associated with a worse prognosis (HR=1.82; 95% CI=1.04-3.19).	<a href="https://pubmed.ncbi.nlm.nih.gov/30089599/">https://pubmed.ncbi.nlm.nih.gov/30089599/</a>	September 2018
8	Clinical management guidelines	NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer (NCCN, 2020)	The NCCN guidelines outline that assessment of the following genomic alterations should be performed as part of the diagnostic work-up of NSCLC patients: EGFR, ALK, ROS1, BRAF, KRAS and MET.	<a href="https://www.nccn.org/professionals/default.aspx">https://www.nccn.org/professionals/default.aspx</a>	15 May 2020

**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.	Clinical validation study	Validation report for detection of MET Exon 14 skipping in FFPE lung adenocarcinoma samples using ion torrent Oncomine Focus Assay	Details the validation study for detection of METex14 skipping in FFPE NSCLC samples using Oncomine Focus Assay.	N/A (internal validation report)	N/A

## 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):

REDACTED

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

Not applicable

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

REDACTED

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

In Australia, there is no single sponsor for detecting METex14 alterations.

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:**

Non-small cell lung cancer represents the main histological type of lung cancer (85%-90%). For therapeutic purposes, NSCLC can be broadly categorised into two further histologic subtypes: squamous (15%-25%) and non-squamous (75%-85%). Non-squamous can be further differentiated (Wender et al., 2013):

- a. Adenocarcinoma is the most common form, accounting for 30 percent of all cases overall and about 40 percent of all NSCLC occurrences. It begins in mucus-producing cells and is more often found in outer part of the lungs in glands that assist with breathing. Symptoms include coughing, hoarseness, weight loss and weakness.
- b. Large cell undifferentiated carcinoma. This type of lung cancer usually accounts for 10 to 15 percent of all cases of NSCLC. It tends to grow and spread quickly and can be found anywhere in the lung. The cancer cells are not always clearly squamous or adenocarcinoma.

Lung cancer is the most common cause of cancer death worldwide accounting for an estimated 1.6 million deaths each year (Torre et al., 2015). Lung cancer was the fifth most commonly diagnosed cancer in Australia in 2015. In 2015, there were 11,788 new cases of lung cancer diagnosed in Australia (6,779 males and 5,009 females). In 2019, it was estimated that 12,817 new cases of lung cancer were diagnosed in Australia (7,184 males and 5,633 females). In 2019, it was estimated that the risk of an individual being diagnosed with lung cancer by their 85th birthday would be 1 in 17 (1 in 15 males and 1 in 21 females). (<https://www.aihw.gov.au/>).

The MET gene is located on human chromosome 7 (7q31), includes 21 exons and 20 introns, and encodes a protein with an apparent molecular weight of 190 kDa. MET is a receptor tyrosine kinase normally expressed by epithelial cells, and is also found on endothelial cells, neurons, hepatocytes, and hematopoietic cells (Salgia, Sattler, Scheele, Stroh, & Felip, 2020). Following transcription of the MET gene, the 21-exon precursor messenger ribonucleic acid (RNA) is spliced, guided by specific sequences in the 5' and 3' introns. Somatic mutations within intronic regions flanking Exon 14 have been identified that can lead to the deletion (or skipping) of exon 14 during transcription. A mutation in one of the exon 14 splice regions located within the exon-intron boundaries results in skipping of exon 14 during splicing. MET Exon 14 mutation hotspots occur, although additional genomic alterations within exon 14 have also been reported. This results in an in-frame deletion of 141 base pairs leading to translation of a shortened MET receptor lacking the juxtamembrane domain on the cytoplasmic side of the plasma membrane. The resulting shortened MET receptor retains affinity for hepatocyte growth factor (HGF) site with a transmembrane region with residual catalytic activity. Mutations in MET causing exon 14 skipping include a variant in the 5' splice site junction of MET exon 14, a 22-base-pair deletion in the 5' splice site junction of exon 14, a 28-base-pair deletion in the 3' splice site, and a point mutation in the 3' splice site (Salgia et al., 2020). Genome profiling of 38,028 tumour specimens from unique patients, identified 224 mutations responsible for MET Exon 14 transcripts, including 126 distinct sequence variants in 221 specimens (Frampton et al., 2015).

Comprehensive genomic profiling of 11,205 lung cancers identified 298 MET Exon 14 NSCLC samples (2.7%) (Schrock et al., 2016). MET exon 14 skipping was most frequently detected in patients with adenosquamous (8.2% of 98 samples) or sarcomatoid (7.7% of 104 samples) histologies. In patients with adenocarcinoma (n = 7149), squamous cell carcinoma (n = 1206), or NSCLC histologic subtype not otherwise specified (n = 1659), MET Exon 14 skipping was detected in 205 (2.8%), 25 (2.1%), and 49 (3.0%), respectively. MET exon 14 skipping was also reported in patients with large cell NSCLC (0.8%) or SCLC (0.2%). In a large cohort of Chinese patients with NSCLC, MET Exon 14 skipping rates were 2.6% in adenocarcinoma, 4.8% in adenosquamous carcinoma, and 31.8% in sarcomatoid carcinoma (Tong et al., 2016).

Overall, the MET Exon 14 skipping alteration (METex14sk) occurs in ~3 to 5% of NSCLC cases, usually in the absence of other oncogenic alterations such as KRAS or EGFR activating mutations, or ALK fusions. Somatic mutations within intronic regions flanking Exon 14 have been identified that can lead to the deletion (or skipping) of exon 14 during transcription.

MET Exon 14 skipping and high-level MET amplification have been reported to be independent prognostic factors of poor survival in multivariable analysis. The prognosis of NSCLC patients with MET dysregulation due to MET Exon 14 skipping, MET amplification or both, appears to be inferior with overall evidence supporting MET Exon skipping alterations being associated with poorer outcomes in patients with NSCLC (Awad et al., 2019).

PD-L1 expression of 0%, 1-49%, and 50% were 37%, 22%, and 41%, respectively in 111 evaluable tumour samples with MET Exon 14 mutations in NSCLC. The median tumour mutational burden (TMB) in METex14-altered lung cancer tumours was lower than that of unselected NSCLC in two independently evaluated cohorts: 3.8 vs 5.7 mutations/megabase and 7.3 vs 11.8 mutations/megabase. For immunotherapy, in response-evaluable METex14-altered patients (n= 24), the ORR was 17% and the median PFS was 1.9 months. Responses were not increased in tumours with PD-L1 expression 50% nor high TMB (Sabari & Paik, 2017)

Therapies for the treatment of patients with NSCLC are part of a highly competitive and dynamic market (e.g. Immunotherapies (IOs) have recently transformed the landscape). Increasingly, the selection of the most appropriate treatment is informed by molecular testing. There is a need for a targeted medicine effective in patients with a diagnosis of NSCLC and METex14 skipping alterations, who have a poor prognosis. The Merck product, tepotinib, is such a treatment.

**REDACTED**

**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:**

The proposed medical service is the testing of tumour material in patients with NSCLC to detect MET Exon 14 skipping alterations, to determine eligibility for treatment with TEPMETKO® (tepotinib) through the PBS.

Who to test:

Target patients for tepotinib treatment are those with locally advanced or metastatic disease. Unlike patients with other oncogene-driven forms of NSCLC (e.g. ALK, EGFR and ROS-1), patients with MET Exon 14 skipping mutations are typically 70 years of age or older (Paik et al., 2020).

The MET Exon 14 skipping alteration occurs in ~3-5% of NSCLC cases, usually in the absence of other oncogenic alterations such as KRAS or EGFR activating mutations, or ALK fusions. The potential population of patients with METex14 mutations in Australia is approximately n~150 per year. This could increase per year, as described in question 49. All NSCLC patients would need to be screened/tested for this mutation once a negative EGFR test has been received.

How the patient is managed and referred:

Lung cancer may be detected due to symptomatic presentation to a General Practitioner (GP), who will start the testing process or due to abnormal findings being detected due to screening. Regardless of how the tests are initiated, the process is the same. A series of tests are completed to identify or diagnose NSCLC (Cancer Council Australia, 2019) is primarily detected using imaging techniques and through the analysis of tissue specimens obtained through biopsies (Cancer Council Australia, 2019).

Patients with known or suspected lung cancer are likely to be offered a contrast-enhanced chest computed tomography scan. Other imaging tests such as a chest X-ray can also be used to detect possible lung nodules (Ettinger et al., 2016) If the tests show that a person has lung cancer, further tests are done to assess the extent of the disease. The test results will show the type of lung cancer and the rate and extent of tumour growth (Cancer Council Australia, 2019).

In Australia, tumour tissue samples are collected by a respiratory physician/surgeon/interventional radiologist as part of routine clinical practice during the initial diagnosis of NSCLC patients. Biopsy samples for pathology testing will often be taken during initial diagnosis of disease and be collected using a range of techniques including bronchoscopy; percutaneous transthoracic fine needle aspiration; and percutaneous transthoracic core biopsy. The tissue samples acquired from biopsy are then sent to the pathologist who performs and interprets the laboratory testing.

Patients with advanced NSCLC are referred to a medical oncologist for ongoing management. The treatment for lung cancer largely depends on the stage of the disease, the location of the cancer and the severity of symptoms and may involve surgery, radiofrequency ablation, chemotherapy, radiotherapy, targeted therapy and immunotherapy.

NSCLC is less likely to develop metastases, but it also less responsive to chemotherapy and radiation therapy compared with SCLC, making surgery the standard first line treatment option for patients with resectable disease, followed by chemotherapy. Local control can be achieved with radiation therapy in a large number of patients with unresectable disease, but cure is seen only in a small number of patients. Patients with locally advanced unresectable disease may achieve long-term survival with radiation therapy combined with chemotherapy. Patients with advanced metastatic disease may achieve improved survival and palliation of symptoms with chemotherapy, targeted agents, and other supportive measures(Ettinger et al., 2016).

**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):**

Molecular alterations that predict response to treatment have been found to be present in approximately 30% of patients with NSCLC and targeted therapy for these alterations improves progression-free survival (PFS) compared with cytotoxic chemotherapy (Arbour & Riely, 2019). Consequently, diagnostics are increasingly approved for use with targeted therapies.

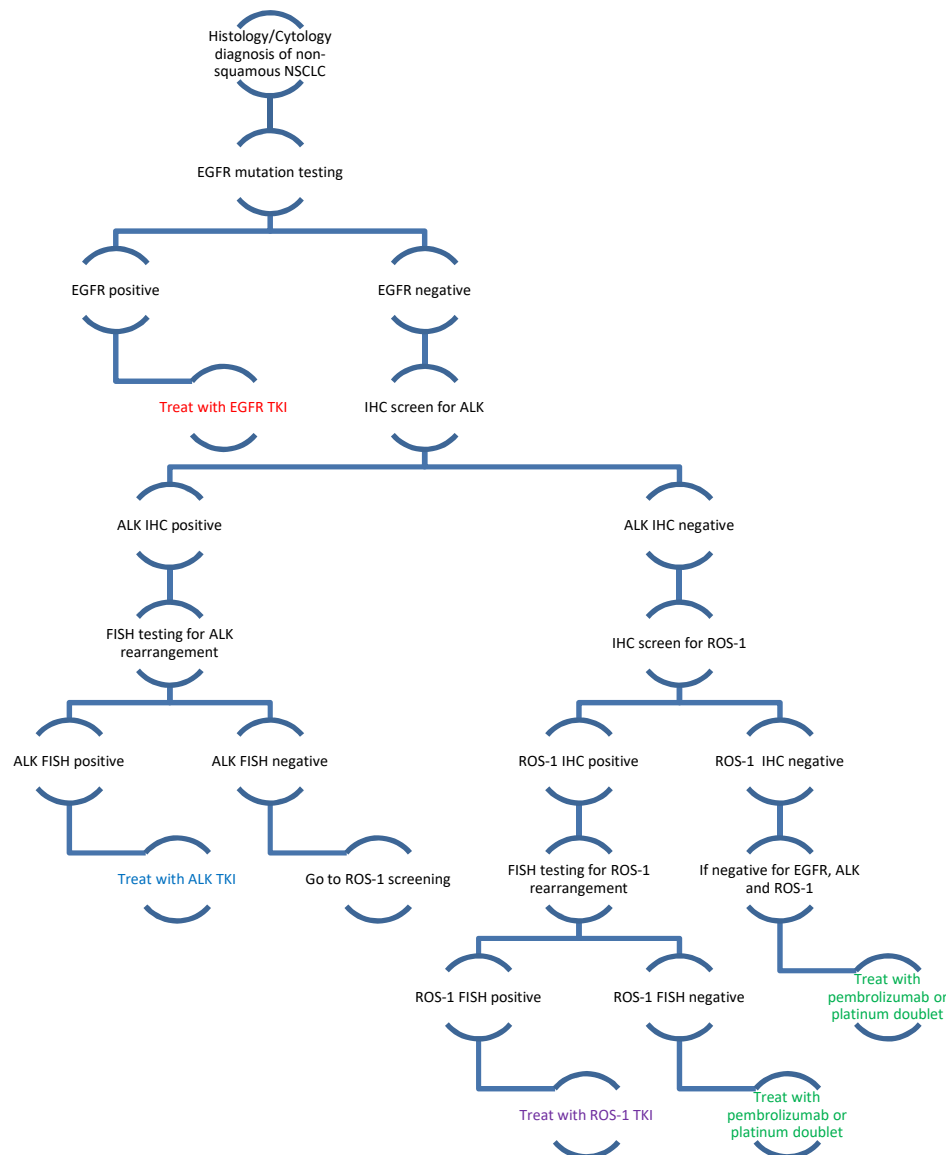
Molecular testing of the biopsy sample may be tested for genetic changes or specific proteins in the cancer cells (biomarkers)(Cancer Council Australia, 2019). Molecular characterisation allows a personalised approach to patient treatment through the better understanding of probable disease risk, prognosis and response to treatment. Guidelines recommend that molecular testing is performed at the time of metastatic NSCLC diagnosis, following histological analysis (Lindeman et al., 2018)

Currently, testing occurs in patients with non-squamous or not otherwise specified NSCLC to determine eligibility for PBS-listed targeted therapies, including tyrosine kinase inhibitors targeting EGFR, ALK and ROS-1. Eligibility for treatment of metastatic NSCLC with pembrolizumab also requires confirmation of the absence of EGFR, ALK and ROS-1 mutations.

As written, eligibility for reimbursement of testing under the available MBS items follows a hierarchical pathway (see Figure 1). In practice, the IHC testing of ALK and ROS-1 could more efficiently be conducted concurrently.

Patients who are ineligible for treatment with the targeted tyrosine kinase inhibitors or pembrolizumab would be given standard of care for advanced non-squamous NSCLC, typically a platinum doublet in the first line setting (commonly carboplatin plus gemcitabine) followed by pemetrexed or docetaxel in the second line.

**Figure 1: Current test and treatment algorithm for advanced NSCLC**



Note: pembrolizumab is listed for treatment naive patients with metastatic NSCLC, negative for EGFR, ALK or ROS-1 and WHO performance status of 0 or 1.

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

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

Validated in-house IVD or commercial IVD tests capable of detecting METex14 skipping alterations using nucleic acid samples is recommended to identify the patients who may benefit from targeted therapy. NATA-accredited in-house IVD tests for METex14 alterations available in Australia may utilise RNA/DNA FFPE tissue depending on the testing platform used.

Nucleic Acid testing is recommended to identify the maximum number of patients who may benefit from targeted therapy. DNA testing identifies mutations (SNPs and small insertion/deletions) that affect the splice site region but does not identify larger deletions. DNA testing will also identify the MET p.Y1003 and MET p.R1004G variants, whereas RNA testing identifies larger deletions that result in MET Exon 14 skipping. The identification of DNA mutations in the MET gene are used to infer the effect on the transcript and predicted to produce a MET Exon 14 skipping variant, however not all variants may be clinically significant. RNA sequencing or RNA PCR based assays test for the RNA transcript directly without having to infer the change in the transcript.

MET Exon 14 testing is not routinely performed in Australia, although a select number of laboratories are currently offering MET Exon 14 testing. Merck is aware of METex14 testing through Genomics for Life, Sonic Genetics, Australian Clinical Labs, Genomic Diagnostics (Healius) and a number of public laboratories using NGS. Merck is also aware of the recently announced Roche collaboration with the Federal Government to fund genomic (NGS) testing for 1000 advanced lung cancer patients.

There are three broad groups of instrumentation.

1. Real-time PCR:

These instruments are standard equipment for a molecular pathology laboratory and the fluorescent probes used for the AmoyDx MET mutation testing kit (FAM and VIC) are standard methods of detection. This specific assay is compatible with a number of instruments including the ABI7500, SLAN-96S, Rotor-Gene Q, Mx3000P and Lightcycler 480 II.

2. NGS (Illumina)

There are a number of different instruments and different assays that can be utilized using this platform. Whilst the standard assays are DNA based, there are also assays that utilize RNA for the detection of gene fusions. In addition, the ArcherDx MET assay is performed using the Illumina platform. A version of the Oncomine Focus Assay (OFA) can also be run on this platform.

Illumina instruments are distributed across Australia and cover both private and public laboratories.

3. NGS (Thermo Fisher)

The NGS instrumentation includes a number of different options. The assays are amplicon based and include Oncomine assays, with the Oncomine Focus assay (OFA) which was used for the tepotinib clinical trial, being part of this group. This assay includes both a DNA and RNA component. Amplicon based assays are faster to perform than hybrid-capture based assays and also have increased sensitivity enabling the use of samples with limited tumour content.

Whilst Thermo Fisher instruments are less common in Australia, again these instruments are distributed across private and public laboratories.

It is proposed to implement sequential MET Exon 14 testing after receiving a negative EGFR test result for NSCLC. This enables the maximum number of patients to be tested and integrates into the current algorithm.

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

Not applicable

**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):**

Accessibility to the test may be limited by a lack of availability in rural and remote locations. In this case samples would be sent to the nearest testing centre of excellence.

Testing would normally be one test per patient, and it is expected that MET Exon 14 skipping variants are stable, although acquired variants may occur during treatment that are associated with targeted therapy resistance (Heist et al., 2016). Retesting may be required if there is insufficient tissue and/or quality of the tumour sample.

The Australian Clinical Practice Guidelines (Cancer Council Australia, 2019) (currently undergoing a staged revision and updating process) make limited recommendations regarding mutation testing, and rather only comment on the specimen types suitable for mutation testing. In summary, the guidelines note that there is generally high concordance in the mutation status of tumours obtained by using samples from histology or cytology samples, or from primary tumours versus metastases and recommend (Grade C) that any tumour sample can be used for mutation testing (sample from primary or metastatic site; histology or cytology sample). In practice, it is advisable to use the optimal specimen available from each patient for mutation testing, assuming more than one specimen is available. This would be the specimen with the highest content and proportion of tumour cells and could be a histology specimen such as a core biopsy or a cytology specimen. This should be determined on a case by case basis by a pathologist.

Despite broad agreement regarding the importance of biomarker testing for patients with NSCLC, variable uptake has been observed in clinical practice. In an observational study of molecular testing and treatment patterns for patients with advanced NSCLC, the rate of molecular testing, primarily EGFR, reported in Australia was 71% (Pennell, Arcila, Gandara, & West, 2019). A number of barriers to the uptake of testing have been suggested including tissue samples being sufficient for diagnosis but inadequate for biomarker testing requiring re-biopsies that may be challenging from a risk, cost, and patient preference perspective.

**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:**

Tumour samples are already routinely collected for the existing genetic assessments used in treatment decision-making for advanced NSCLC patients (EGFR mutations and ALK or ROS-1 rearrangements). Under the proposed algorithm, MET Exon 14 assays would be conducted sequentially upon receiving an EGFR negative assay test result and before any testing for ALK/ROS-1 mutations. It is anticipated that the test requirements would be similar (i.e. use of PCR/NGS) for EGFR and MET Exon 14 testing. Although officially classed as a sequential test, Merck understand that the MET Exon 14 test would be completed before any treatment commences and before any testing of ALK/ROS-1. It is important to emphasise that there would be no treatment between receiving a negative EGFR test and the results of the MET Exon 14 test. Patients testing positive for EGFR or MET exon 14 skipping alterations will be treated accordingly and not tested further for ALK or ROS-1 rearrangements. This would reduce the quantity of IHC and/or FISH testing conducted to determine the presence of ALK/ROS-1 rearrangement, but given the low prevalence of MET exon 14 skipping alterations, the reduction in ALK and ROS assays would be small.

It is proposed to conduct the MET Exon 14 assay sequentially with the EGFR assay being completed first for NSCLC and then the MET Exon 14 upon receipt of an EGFR negative assay test. This would enable the maximum number of patients to be tested and integrated into the current algorithm. Similarly, this would improve efficiencies in terms of time, cost and the availability of suitable tumour tissue samples and potentially reduce the rate of block recall to extract further tissue for further assays.

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

A request for testing for genomic alterations in tumour tissue from a NSCLC patient would be initiated by the patient's managing clinician, most likely a medical oncologist or thoracic medicine specialist.

Testing should be conducted in laboratories holding the appropriate accreditation and registration for this diagnostic testing procedure.

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

Testing should be conducted, and results interpreted by qualified and trained pathologists. The immediate testing of tissue for MET Exon 14 skipping alterations can commence immediately upon the receipt of an EGFR negative test if the test is classed as pathologist determinable.

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

As above.



**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 will be performed in laboratories that have received National Association of Testing Authorities (NATA) accreditation under an appropriate Quality Assurance Program.

**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

**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):**

Testing to detect METex14 skipping alterations is not currently funded by the Commonwealth for patients with NSCLC.

Therefore 'no testing' is the comparator.

Patients who are found to be ineligible for targeted therapy with tyrosine kinase inhibitors (EGFR/ALK/ROS-1) would receive treatment with an immuno-oncology drug (pembrolizumab first line in treatment naïve patients with metastatic NSCLC, with no evidence of an activating EGFR gene or an ALK gene rearrangement or a ROS1 gene rearrangement in tumour material) or platinum doublet chemotherapy. In the second line, patients may be offered treatment with nivolumab after failure of platinum-based chemotherapy, or pemetrexed/docetaxel.

**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

Not applicable

- 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):**

The comparator for the proposed diagnostic test for MET Exon 14 skipping alteration is “no test.” Therefore the clinical management is as depicted in Figure 1 (Q26).

- 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:**

Not applicable

- 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):**

It is proposed that the assay to detect MET Exon 14 skipping alterations be conducted sequentially upon receiving an EGFR negative assay test result and before any testing for ALK/ROS-1 mutations. This ensures the maximal number of patients tested at the lowest cost to the Medicare system. It is expected that the testing numbers would be similar to those for EGFR testing with the potential for an increase in numbers during the first 6 months due to catch-up testing. As a pathologist determined test, the immediate testing of tissue for MET Exon 14 skipping alterations can commence immediately upon the receipt of an EGFR negative test. This is expected to be a less expensive option with reduced repeat biopsy rates and improved tissue utilization. This option also improves the turnaround time and reduces patient loss due to more complicated logistics of requiring different tests and facilities.

**Figure 2: Test and treatment algorithm for advanced NSCLC after inclusion of testing for MET ex 14 skipping alterations**



**PictureNote:** Inclusion of test for MET exon 14 skipping alterations would cause downstream changes to the MBS and PBS restrictions for ALK TKI, ROS-1 TKI and pembrolizumab, to include requirement for prior test for MET ex 14 in the testing and PBS eligibility wording.

**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 overall clinical claim is that the proposed co-dependent technologies (testing of tumour material in patients to detect MET exon 14 skipping alterations and tepotinib therapy) will be non-inferior in terms of comparative effectiveness versus the main comparator (no testing and current standard of care) in patients with advanced NSCLC.

This will be explored in more detail in the submission and may change to superior once more data is analysed. Currently there is no clinical care specifically targeted at patients with the MET Exon skipping alterations.

**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:** Safety and tolerability of tepotinib treatment assessed by AEs, physical examinations, laboratory findings, and vital signs.

**Clinical Effectiveness Outcomes:**

**Drug outcomes**

Objective response rate (ORR)

Overall survival (OS)

Progression-free survival (PFS)

Partial response (PR)

Complete response (CR)

Health-related quality of life (HRQoL)

**Test outcomes**

*Trial based (evidentiary standard) analytical performance:*

Sensitivity

Specificity

Positive predictive value (PPV)

Negative predictive value (NPV)

*Clinical utility of test:*

Predictive effect of testing of tumour material in patients to detect MET exon 14 skipping alterations and prescribe tepotinib therapy.

Treatment effect modification of tepotinib in patients in patients with advanced NSCLC.

*Other test-related considerations:*

Re-biopsy rates

Test turn-around time

Estimated number of patients being tested

Number needed to test

Cost of testing per patient

## PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

Non-small cell lung cancer represents the main histological type of lung cancer (85%-90%). For therapeutic purposes, NSCLC can be broadly categorised into two histologic subtypes: squamous (15%-25%) and non-squamous (75%-85%). Adenocarcinoma is the most common form of non-squamous NSCLC, accounting for 30 percent of all cases overall and about 40 percent of all NSCLC occurrences.

#### Incidence of lung cancer and NSCLC in Australia

The number of incident lung cancer cases in Australia in 2018 was 13,168 (Globocan) and NSCLC encompasses approximately 85%–90% of all lung cancers<sup>1</sup>, and these data can be used to calculate the incidence of NSCLC in Australia: Estimated incidence of NSCLC (Australia) = 0.9 x 13,168 = 11,851 cases.

#### Proportion of NSCLC with *METex14* skipping alterations

There are no specific publications on the proportion of NSCLC with *METex14* skipping alterations for Australia. In US-based studies with routine detection of *METex14* alterations in lung cancer patients, the prevalence of *METex14* alterations has been reported at around 3% (Awad et al., 2019; Sabari et al., 2018; Schrock et al., 2016). Internal audit data from a local laboratory in Australia indicates that the prevalence of *METex14* alterations is around REDACTED, which seems to be similar to that reported in other literature (Sabari et al., 2018). A conservative approach is used in which it is assumed that the prevalence of *METex14* alterations is as high as 5.1% in NSCLC (Sabari et al., 2018).

#### Mean disease duration

Mean disease duration is given as median overall survival for patients with NSCLC. In the publications from the US shown above (Sabari 2018), the median overall survival was less than a year. In a conservative estimate, we assume average median overall survival of 2 years (Scenario 1) or 5 years (Scenario 2) for patients in Australia with NSCLC (Table 1).

Prevalence calculation: Estimated prevalence = Incidence of NSCLC x median duration of disease.

Conclusion: The prevalence of NSCLC patients harbouring *METex14* alterations in Australia is < 5 per 10,000 (Table 1).

**Table 1: Estimated prevalence of NSCLC with *METex14* skipping alterations in Australia<sup>2</sup>**

	Estimated prevalence (n)	Australia population size	Prevalence per 10,000
<b>Scenario 1</b>	P = 11,851*2 = 23,702 NSCLC cases*0.85 (EGFR neg results) *0.051 with <i>METex14</i> alterations = 1,027 cases	25,464,116 as of 30 Sept 2019	1,027/25,464,116 * 10,000 = 0.4/10,000
<b>Scenario 2</b>	P = 11,851*5 = 59,255 NSCLC cases*0.85 (EGFR neg results) *0.051 with <i>METex14</i> alterations = 2,568 cases		2,568/25,464,116 * 10,000 = 1/10,000

The potential population of patients with *METex14* skipping alterations in Australia is approximately n=~150 per year). Nevertheless, all EGFR negative NSCLC patients would need to be screened/tested (5% incidence rate) for this mutation.

<sup>1</sup> <https://lung-cancer.canceraustralia.gov.au/types>

<sup>2</sup> <https://www.abs.gov.au/AUSSTATS/abs@.nsf/mf/3101.0>

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

It is expected that testing for MET Exon 14 would be conducted only once per patient.

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

The testing would normally be one test per patient, and it is expected that MET Exon 14 skipping variants are stable, although acquired variants may occur during treatment that are associated with targeted therapy resistance (Heist et al., 2016).

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

Testing is already performed for EGFR and sequential testing can be incorporated into this process. It is estimated there will be 4544 NSCLC cases tested for EGFR in 2020 which is a slight decrease from 2019. For EGFR testing there were 1451 cases in 2014, 3368 in 2015, 3419 in 2016, 3863 in 2017, 4147 in 2018 and 4603 in 2019 (Medicare statistics). The predicted numbers from the MSAC Application 1516 are realistic for the number of NSCLC cases. Based on these numbers, the estimated patient population by year to be treated with METex14 skipping alterations in Australia is shown in **Table 2: Potential patient population by year to be treated with METex14 skipping alterations in Australia.**

**Table 2: Potential patient population by year to be treated with METex14 skipping alterations in Australia**

Year	EGFR population (Medicare statistics)	METex14 testing population (85% of the EGFR potential population – 15% are expected to be EGFR positive)	METex14 potential population (3 to 5% of testing population will be positive)
2014	1451	1233	37 to 62
2015	3368	2862	86 to 143
2016	3419	2906	87 to 145
2017	3863	3283	98 to 164
2018	4147	3525	105 to 176
2019	4603	3912	117 to 195
2020	4544	3862	116 to 193
			Average: 92 to 154

For the first 3 months of 2020, 1136 EGFR tests were performed with an estimated total number of 4544 tests for 2020, however this may be impacted by Covid-19. This data indicates a relatively rapid uptake of testing with a gradual increase over time associated with an increase in the number of cases. The addition testing for METex14 to testing for EGFR is not expected to result in a significant increase in the number of samples with insufficient tissue.

The EGFR positive rate is 15%, as accepted in the MSAC application 1516 For sequential testing In approximately 15% of NSCLC patients, the tumour harbours a mutation in the EGFR gene, which confers sensitivity to EGFR tyrosine kinase inhibitors (EGFR TKIs).<sup>3</sup> If the proposed sequential testing option is approved where immediately testing for METex14 occurs upon receiving an EGFR negative result, before any treatment commences, then the uptake is expected to be high. This will be the case if the test is pathologist determinable which enables reflex testing to be ordered without a delay in the requiring a specialist referral. A loss of patients is expected due to insufficient tissue for sequential testing, and this is estimated to be 10%. However, a number of patients would have a repeat biopsy and would be subsequently captured and tested.

<sup>3</sup> Peters, M.J., et al., Outcomes of an Australian testing programme for epidermal growth factor receptor mutations in non-small cell lung cancer. Intern Med J, 2014. 44(6): p. 575-80.

It is estimated that there would be 100% of tests completed in year one for people with advanced lung cancer and 85% in year two. The higher numbers in year one are due to catch-up testing to be performed for patients who have not been tested for *MET* Exon 14 variants. If the sequential testing is performed the uptake should be similar to that for the current EGFR testing if the same tissue is used for both tests. Numbers could be lower due to loss of patients due to failure to order sequential tests.

The estimated total number of patients for targeted therapy is approximately 150 patients each year. This does not include catch up patients. If an early access program is initiated, then it is expected that the catch-up patients would be identified and tested during that phase. The estimated numbers would be 70% for the first year for sequential testing with no catch-up increase. It is not expected to change significantly over time.

Once a *MET* targeted therapy is approved by TGA, it is expected that very small numbers of patients will request testing for *MET* Exon 14 prior to MSAC approval.

**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:**

It is not anticipated that there would be any supply or demand issues as the overall number of patients requiring testing to detect *MET* Exon 14 is manageable even if the number of laboratories conducting testing does not increase. Risk of leakage is expected to be low given the specific details of the proposed item descriptor.

A detailed utilisation analysis will be presented in the co-dependent MSAC/PBAC submission.

## PART 8 – COST INFORMATION

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

### Costings for sequential testing:

**REDACTED.** Whilst the test is only testing a single gene, there is a large number of variants that are required to be covered. If RNA testing is performed this requires a separate testing methodology as DNA is used for EGFR testing. Extraction may be performed using a kit for simultaneous DNA and RNA extraction or separate extractions for DNA and RNA. The methodology used has an implication for tissue utilization and the number of repeat biopsies.

Current item numbers and Prices (100% MBS):

- 73337 EGFR \$397.35
- 73351 EGFR T790M \$397.35
- 73341 ALK FISH \$400
- 73344 ROS1 FISH \$400
- 73338 RAS \$362.60
- 73336 BRAF \$230.95
- 73374 Multiple genes One gene \$340
- 73375 Multiple genes 2 or 3 genes \$400
- 73376 Multiple genes 4 or more genes \$800
- 73377 FOXL2.402C>G status \$250
- 73378 NUTM1 gene status \$340
- 73379 ETV6-NTRK3 gene rearrangement \$340
- 73380 MAML2 gene rearrangement \$340
- 73381 ETV6-NTRK3 salivary gland \$340
- 73382 EWSR1 gene rearrangement \$340
- 73383 TFE3 gene rearrangement ± TFE3 gene rearrangement \$400

**Table 3: Current estimated cost of NSCLC testing excluding PD-L1 immunohistochemistry**

Item Number	2018	2019	2020 Jan-Mar	Estimated 2020	Fee 85%	Estimated Cost 2020
73337 -EGFR	4147	4603	1136	4544	\$337.75	\$1,534,736.00
73341-ALK FISH	292	201	51	204	\$340	\$69,360.00
73344-ROS1 FISH	0	121	72	288	\$340	\$97,920.00
72860-Block Retrieval	0	327	660	2640	\$72.25	\$190,740.00
						\$1,892,756.00
IHC assuming from 72848 to 72847				4544	\$25.30	\$114,963.20
						\$2,007,719.20

**Table 4: Estimated cost of sequential testing for MET Exon 14 skipping**

**REDACTED**

### Cost per patient:

At 100% of MBS the estimated cost per patient for the current testing protocol is **REDACTED**.

For the sequential model, the estimated cost per patient is **REDACTED** if an addition fee of **REDACTED** is added **REDACTED**. These costings include block retrieval costs in addition to the actual costs of testing.



An economic model comparing different types of genetic testing in metastatic non-small lung cancer (NSCLC) found using next-generation sequencing to test for all known lung cancer-related gene changes (EGFR, ALK, ROS1, BRAF, MET, HER2, RET and NTRK1 plus KRAS) at the time of diagnosis was less costly and faster than sequentially testing one of a limited number of genes at a time (Pennell et al., 2019).

In the model, patients with newly diagnosed met metastatic NSCLC received PD-L1 testing and testing for the known lung cancer-related genes using one of four different approaches:

- Upfront next generation sequencing (all eight NSCLC-related genes and KRAS were tested at once)
- Sequential tests (one gene at a time was tested)
- Exclusionary KRAS test followed by sequential tests for changes in other genes if KRAS was not mutated (if KRAS mutations were found, the tumour was not tested for other mutations because it is rare to have more than one of these genes mutated in an individual lung cancer)
- Panel test (combined testing for EGFR, ALK, ROS1 and BRAF), flowed by either single-gene or next-generation sequencing test for changes in other genes.

A significant amount of tumour tissue is consumed by standard “piecemeal” non-NGS testing, with the majority of patients (84%) requiring two or more biopsies to complete both non-NGS and NGS testing (Drilon et al., 2014; Naidoo, Page, & Wolchok, 2014). 69% (n=18/26) underwent multiple biopsies in order to complete non-NGS testing alone. In a study of 22 NSCLC specimens using NGS, 5 (22.7%) were surgical resections and 17 (77.3%) were small biopsy and cytology specimens. Twenty-one (95%) of the specimens were adequate for full sequencing. With the next-generation sequencing, patients initiated appropriate therapy 2.8 and 2.7 weeks faster than sequential or exclusionary testing, respectively (Pennell et al., 2019).

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

For a standard EGFR mutation test, the time taken in a laboratory to perform the test is:

- NGS: 5-10 Days

It is anticipated there would be a similar turnaround for the MET Exon 14 test

**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 or 7 – Pathology or genetics services
<p>Proposed item descriptor: Proposed item descriptor: 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, and with documented absence of activating mutations of the epidermal growth factor receptor (EGFR) gene, requested by or on behalf of, a specialist or consultant physician or determinable by a pathologist, to determine:</p> <p>If the requirements relating to MET exon 14 skipping gene status (including deletion mutations) for access to tepotinib are fulfilled under the Pharmaceutical Benefits Scheme (PBS)</p> <p>Fee: <b>REDACTED</b> Benefit: 85% = <b>REDACTED</b></p>

Testing for MET Exon 14 would be conducted sequentially to the EGFR test, if the EGFR result is negative and prior to any treatment

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