Australian Government
Department of Health

MSAC Application 1634

Comprehensive genomic profiling of non-small cell lung cancer tumour tissue specimens using next generation sequencing assays

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 in order 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.

Phone: +61 2 6289 7550
Fax: +61 2 6289 5540
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):

This application has been prepared as a partnership between Roche Products (Roche Pharmaceuticals) and Roche Diagnostics.

Corporation name: Roche Products Pty Limited

ABN: 70 000 132 865

Business trading name: Roche Products

Corporation name: Roche Diagnostics Australia Pty Limited

ABN: 29 003 001 205

Business trading name: Roche Diagnostics

Primary contact name: REDACTED

Primary contact numbers

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?

N/A

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Comprehensive genomic profiling of non-small cell lung cancer tumour tissue specimens using next generation sequencing assays

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

Lung cancer is the fifth most commonly diagnosed cancer in Australia. Based on projections of lung cancer incidence outlined in the background document to the PD-(L)1 checkpoint inhibitor stakeholder meeting (DoH 2019) there will be 12,990 new cases of lung cancer in Australia in 2020. There are two broad classes of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). This application is focused on NSCLC.

Patients with NSCLC that are diagnosed early may be managed by surgical removal (resection) of their tumour. In circumstances where surgical resection is not appropriate due to advanced disease, or when a patient experiences disease progression following surgical resection, management with systemic therapy is recommended. The selection of the appropriate systemic therapy to use in NSCLC patients is increasingly being guided by the identification of molecular biomarkers in a patient's tumour. This application relates to the use of comprehensive genomic profiling (CGP) of NSCLC tumour tissue using next generation sequencing (NGS) assays in patients being considered for treatment with systemic therapy.

Note: Next generation sequencing assays may be used to identify molecular alterations from DNA or RNA extracted from multiple tumour types. This application is focused on patients with NSCLC only. The decision to focus the application on NSCLC was made after a discussion with representatives from the Department of Health during a meeting held 29th May 2018. At this meeting it was suggested that any MSAC application would benefit from focusing on a discrete population. Non-small cell lung cancer is proposed as being an appropriate, high need discrete patient population as there are multiple biomarker tests associated with the identification of multiple treatments currently listed on the Pharmaceutical Benefits Scheme (PBS) or under active clinical development. All molecular biomarker tests currently funded on the MBS for NSCLC patients may be consolidated with the use of a NGS assay.

Based on the results of ongoing clinical trials, the use of CGP in patients with rare cancers, cancers of unknown primary origin, or patients with very late stage disease who have limited treatment options may become established as part of clinical care. In this context, CGP would be used to identify the presence of mutations with a corresponding targeted therapy based on the rationale that patients will achieve better outcomes (in terms of treatment benefit and/or reduced toxicity) if they are matched to a targeted treatment based on the genomic profile of their disease. Roche Products and Roche Diagnostics note that NTRK testing of solid tumours to identify patients eligible for treatment with larotrectinib and microsatellite instability/DNA mismatch repair (MSI/dMMR) testing to identify patients eligible for treatment with pembrolizumab are the basis of current MSAC Applications (application 1602 and 1508). While these molecular alterations may be identified by some NGS assays it is proposed that the use of NGS assays in treatment contexts outside of NSCLC would be the basis of subsequent MSAC assessments.

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)

Next generation sequencing assays facilitate the CGP of tumour tissue through their ability to identify four classes of genomic alterations: base substitutions (single nucleotide variants); insertions and deletions; copy number alterations; and gene fusions (rearrangements).

By simultaneously testing multiple genes for multiple types of genomic alterations, NGS assays provide clinicians with detailed information on the biomarker status of patients, including the presence of genomic alterations for which a targeted therapy is available. The use of CGP using NGS assays is also able

to provide information on genomic signatures including Tumour Mutation Burden (TMB) and microsatellite instability (MSI).

The consolidation of multiple molecular biomarker tests into a single NGS assay avoids the need to perform a sequence of biomarker tests. This may lead to a reduction in the number of procedures performed to obtain further biopsy material when the original sample is depleted.

Note: As part of the reform to the regulatory requirements for IVD medical devices being implemented by the Therapeutic Goods Administration (TGA), an IVD medical device which provides information that is essential for the safe and effective use of a corresponding medicine or biological will be deemed an 'IVD companion diagnostic'. The Instructions for Use (IFU) for IVD companion diagnostics must stipulate how the IVD is intended for use with the corresponding medicine.

The FoundationOne® CDx assay is a NGS assay able to perform CGP using DNA isolated from solid tumour specimens (including NSCLC). This assay is currently FDA-approved as an IVD companion diagnostic to identify patients who may benefit from treatment with a range of targeted therapies. Currently, the testing of tumour specimens using the FoundationOne® CDx assay is performed in centralised laboratories located outside of Australia. On this basis, testing using the FoundationOne® CDx assay would not currently be eligible for funding through the MBS as part of the service is rendered outside of Australia. Foundation Medicine and Roche Sequencing Solutions (Roche Diagnostics) are developing a NGS CGP panel based on the FoundationOne® CDx assay that will enable laboratories to perform CGP locally[1] and be eligible for funding through the MBS.

Roche and Illumina have recently entered into a partnership to develop IVD companion diagnostics for the Illumina NextSeq™ 550Dx System[2]. Through this agreement Roche will develop and commercialise IVD tests based on NGS technologies for use on the Illumina NextSeq 550Dx System.

As per the framework established by the 'Regulatory requirements for in-house IVDs (Version 2.2, September 2018)' published by the Therapeutic Goods Administration (TGA), local laboratories are able to purchase Research Use Only (RUO) products from commercial suppliers and develop an in-vitro diagnostic (IVD) test. The development of an in-house IVD must be undertaken within the framework established by the 'Requirement for the development and use of in-house in vitro diagnostic medical devices (IVDs) (Fourth Edition 2018)' document published by the Department of Health. Alternatively, local laboratories may use any NGS assay which has been included in the Australian Register of Therapeutic Goods (ARTG) as an IVD companion diagnostic per the Instructions for Use (IFU) of the IVD companion diagnostic assay. As such, it is possible for CGP to be undertaken using NGS assays classified as being for RUO or IVD companion diagnostics within the regulatory framework for IVD testing in Australia.

Given the forthcoming availability of multiple commercial CGP NGS assays with IVD companion diagnostic claims and the capacity of local laboratories to develop their own in-house IVD under the regulatory framework established by the TGA it is proposed that the assessment of CGP of tumour tissue from NSCLC patients is not limited to a specific brand of NGS assay. It is anticipated that the evidence supporting the approval of the FoundationOne® CDx assay as an IVD companion diagnostic will represent critical evidence provided to MSAC in the Applicant Developed Assessment Report but that additional evidence relating to the use of CGP using NGS reported for other assays will also be presented for MSAC consideration.

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

☒ Yes
☐ No

[1] https://www.foundationmedicine.com/blog/partnerships-are-paving-the-way-for-improved-patient-options
[2] https://www.roche.com/media/releases/med-cor-2020-01-13.htm

(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:

Not applicable

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

Use of CGP to monitor a patient over time by the detection of minimal residual disease and/or acquisition of mutations conferring resistance to treatment is an area of ongoing research. This MSAC Application Form is focussed on the role of CGP using a NGS assay to identify a NSCLC patient suitable for treatment with a targeted therapy at the time of initiating treatment. It is proposed that the use of CGP using a NGS

assay in the context of monitoring a patient over time may be the basis of a separate MSAC assessment if it is recommended as part of standard clinical management in the future.

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

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

The intended effect is to identify NSCLC patients suitable for treatment with a targeted therapy listed on the PBS.

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):

There are several biomarkers included in commercially developed NGS assays which inform the selection of targeted NSCLC therapies currently listed on the PBS-listed (see below). The biomarkers included in NGS assay developed in-house will be laboratory dependent, however it is reasonable to foresee that that in-house developed NGS assays would include biomarkers which are used to inform the selection of targeted therapies.

Biomarker	PBS therapy	PBS code(s)	Sponsor
EGFR	Erlotinib	10014C; 10019H; 10020J; 10025P; 10028T; 11259N; 11260P; 11263T	Roche
	Gefitinib	11264W; 8769M	Astra Zeneca
	Afatinib	11329G; 11335N; 11336P; 11341X; 113147F; 11348G; 11359W	Boehringer Ingelheim
EGFR T790M mutation positive after prior EGFR targeted treatment	Osimertinib	11620N; 11622Q	Astra Zeneca
ALK	Crizotinib	10322G; 10323H	Pfizer
	Ceritinib	11056X	Novartis
	Alectinib	11226W	Roche
ROS1	Crizotinib	11589Y; 11594F	Pfizer

Recent advances in genomic sequencing technologies have revealed the genetic diversity of lung cancers and led to the identification of oncogenic drivers. In turn, this has led to the development of several new therapies targeting newly discovered oncogenic drivers in lung cancer. An overview of lung cancer biomarkers and associated targeted therapies under clinical investigation which may be considered by the PBAC in the foreseeable future is provided below.

Biomarker	Therapy	Status	Sponsor
EGFR Ex19del, L858R	Osimertinib (first-line)	Under MSAC/PBAC review	Astra Zeneca
	Dacomitinib	Clinical trial reported (FDA approved)	Pfizer
ALK	Brigatinib	PBAC recommended	Takeda
	Lorlatinib (second-line)	PBAC recommended	Pfizer
ROS1	Entrectinib[a]	Under MSAC/PBAC review	Roche
	Lorlatinib	Clinical trial reported	Pfizer
	Cabozantinib	Clinical trial ongoing	Exelixis
	Repotrectinib	Clinical trial ongoing	Turning Point Therapeutics
BRAF	Dabfrafenib+trametinib	Clinical trial reported (TGA approved)	Novartis
RET	Cabozantinib	Clinical trial ongoing	Exelixis
	Vandetanib	Clinical trial ongoing	Astra Zeneca
NTRK	Entrectinib[a]	Clinical trial reported	Roche
	Larotrectinib[a]	Submitted to MSAC for PICO development	Loxo Oncology/Bayer
MET	Cabozantinib	Clinical trial ongoing	Exelixis
HER2 (ERB2)	Ado-trastuzumab emtansine[a]	Clinical trial ongoing	Roche

a: 'Basket' trial of solid tumours including NSCLC

Many of the commercially available NGS assays are able to test for BRAF, RET, NTRK, and MET genomic alterations on the same tumour tissue and at the same time as testing for EGFR, ALK and ROS1 alterations. As such, NGS assays have the ability to offer a 'future proof' biomarker assay for a wide range of targeted therapies for lung cancer which may be considered by the PBAC in the near future.

The simultaneous assessment of multiple molecular biomarkers by NGS assays also helps to preserve biopsy material and has the potential to reduce re-biopsy procedures when the original sample is insufficient or depleted.

The Applicant is seeking that the CGP using NGS assays be assessed as a 'treatment agnostic' testing methodology for NSCLC patients, i.e. the results of testing may be used to identify patients eligible to access all lung cancer treatments targeting a molecular alteration currently listed on the PBS.

As outlined in the 'IVD companion diagnostics, Guidance on regulatory requirements (Version 1.1, February 2020) document published by the TGA, "the TGA will review an application for an IVD companion diagnostic within the context of, and in conjunction with, is corresponding medicine or biological to ensure a comprehensive evaluation of the benefits and associated risks of the therapeutic goods when used for their intended purpose and indication." (p. 10) Under this scenario the TGA will assess the suitability for assays used as IVD companion diagnostics (including the forthcoming assay based on FoundationOne® CDx) to be used to identify patients that are likely to benefit from a targeted treatment.

Under the regulatory framework for the assessment of IVD companion diagnostics it proposed that NGS assays with appropriate regulatory approval as an IVD companion diagnostic could be used to identify patients eligible to access future targeted therapies for NSCLC through the PBS after standard review of the efficacy, safety and cost-effectiveness of the therapy by the PBAC. Under this proposal it is envisioned that the assessment of reimbursement submissions of future targeted therapies for NSCLC may be

considerably streamlined as the assessment of the technical performance characteristics of NGS technology would have been assessed by MSAC through this application and the assessment of the clinical utility of future biomarkers will be conducted by the TGA as part of its assessment of IVD companion diagnostics required to identify patients eligible to be treated with future targeted treatments. In this way there is an opportunity for sponsors preparing reimbursement submissions of targeted NSCLC therapies with a biomarker included in a NGS assay with appropriate regulatory approval to pursue a streamlined co-dependent technology reimbursement pathway by:

- Lodging a major submission to the PBAC presenting evidence of the efficacy, safety, and cost-effectiveness of the targeted NSCLC therapy, and
- Lodging a submission to MSAC requesting an amendment to the MBS item for CGP of NSCLC tumour tissue using NGS assays to include any new biomarker test/treatment combination.

Note: The Applicant would welcome further discussion of the practical implications of the 'treatment agnostic' approach to the MSAC assessment of NGS assays with TGA-approval as an IVD companion diagnostic to be used to test tumour tissue from NSCLC patients with representatives from the Department, PASC, MSAC or the PBAC.

(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

As described above, the Applicant is seeking that NGS assays be assessed as a 'treatment agnostic' biomarker assay for NSCLC patients, i.e. the results of testing may be used to identify patients eligible to access all targeted treatments currently listed on the PBS.

(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

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)?

☐ Yes
☐ No

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

☐ Yes
☐ No

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

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

Multi-use consumables: The conduct of CGP using NGS assays requires the use of several reagents and/or kits for the processing of samples from nucleic acid isolation through to the preparation of an enriched library ready for sequencing. While the reagents/kits associated with a specific NGS assay may differ slightly between manufacturers or in-house assays, the consumables associated with the conduct of CGP using NGS assays are:

- Nucleic isolation reagents
- Reverse transcription reagents (if RNA based sequencing undertaken)
- Library preparation reagents
- Enrichment reagents
- Hybridisation and capture reagents
- Enriched library amplification reagents
- Amplified library clean-up and normalisation reagents

Pathology laboratories would use standard consumable items and equipment during the preparation tissue specimens for CGP using NGS assays.

Sequencing of libraries is performed on a commercially available NGS sequencing platform. It is understood that platforms manufactured by Illumina such as NextSeq 500/550/550Dx instruments are the most commonly used instruments in Australian laboratories.

After the sequencing of libraries has been undertaken bioinformatic processing of sequencing files is required to identify genomic alterations known to be associated with the clinical condition, including the identification of alterations known to confer sensitivity to a targeted treatment.

Following bioinformatic processing the results are reviewed by a pathologist and a report detailing the outcome of CGP using a NGS assay is prepared for the patients treating clinician.

Sequencing data and clinical specimen archiving is also undertaken per the operational requirements for pathology laboratories. These activities require the use of consumables/infrastructure which would be shared with tumour tissue specimens from other cancer types and not necessarily specific to NSCLC specimens that had CGP performed using a NGS assay.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

Type of therapeutic good: In-vitro diagnostic medical device/Research Use Only assay.
Manufacturer's name: This application is not limited to a specific manufacturer. Current manufacturers of NGS assays include Roche Diagnostics, Illumina and Thermo Fisher.
Sponsor's name:

(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

The use of any NGS assay to inform the clinical management of NSCLC patients would result in it being a Class 3 IVD medical device product, noting that the classifications listed above refer to Medical Devices, not IVD Medical Devices.

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

The FoundationOne® CDx assay is available to Australian clinicians and is currently FDA-approved as an IVD companion diagnostic. However, as samples are sent offshore for testing , this assay not currently falls under the jurisdiction of the TGA.

The Intended Use and FDA-approved IVD companion diagnostic indications of the FoundationOne® CDx assay are provided below.

It is anticipated that the forthcoming CGP assay based on the FoundationOne® CDx assay will seek TGA-approval as an IVD companion diagnostic with indications consistent with the FDA-approved indications for FoundationOne® CDx. Please note that the final IVD companion diagnostic indications sought from the TGA will be based on the clinical evidence available to pursue IVD companion diagnostic indications at the time of seeking inclusion in the ARTG.

Intended Use

FoundationOne® CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Table 1. Companion diagnostic indications

Tumor Type	Biomarker(s) Detected	Therapy
Non-small cell lung cancer (NSCLC)	EGFR exon 19 deletions and EGFR exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), Tagrisso® (osimertinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAK V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	BRAK V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAK V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)
Breast cancer	ERBB2 (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
Colorectal cancer	KRAS wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	BRCA1/2 alterations	Lynparza® (olaparib) or Rubraca® (rucaparib)

The test is also used for detection of genomic loss of heterozygosity (LOH) from formalin-fixed, paraffin-embedded (FFPE) ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the RUBRACA product label.

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

Several NGS assays suitable to be used to perform CGP on tumour tissue from NSCLC patients are currently marked as RUO. Examples are the AVENIO Tumor Tissue Targeted Panel (17 genes) and the AVENIO Tumor Tissue Expanded Panel (77 genes) marketed by Roche Diagnostics and the TruSight Oncology 170 (170 genes) and TruSight Oncology 500 (523 genes from DNA and 55 genes from RNA) panels marketed by Illumina

In Australia the use of a NGS assay labelled as RUO to develop an IVD test reporting clinical results would lead to the test being captured by the regulatory framework outlined in the 'Requirement for the development and use of in-house in vitro diagnostic medical devices (IVDs), Fourth Edition 2018' document published by the Department of Health.

Based on the criteria outlined on page 4 of the 'Requirement for the development and use of in-house in vitro diagnostic medical devices (IVDs), Fourth Edition 2018)', Class 1-3 in-house IVDs are exempt from inclusion in the ARTG.

Any laboratory using NGS RUO assays to develop an in-house IVD must be accredited to do so and is required to notify the TGA of the introduction of the IVD by 1 July of the next financial year.

The responsibility for notifying the TGA of the development of an in-house IVD based on a RUO assay lies with the laboratory which has developed the in-house IVD and not the commercial manufacturer of the RUO assay. As such, it is not possible to provide information regarding where any given laboratory would be in the process of notifying the TGA of their development and use of an in-house IVD from a RUO assay.

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

Unknown, refer to previous response.

PART 4 – SUMMARY OF EVIDENCE

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

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*** **
1	Clinical validation study	Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing: (Frampton et al. 2013)	Details the development and validation of the FoundationOne assay. The diagnostic accuracy of FoundationOne was compared with established assays assessed on 249 tumour tissue specimens. The results of CGP on 2,221 solid tumour clinical cases (including 400 lung cancer cases) are also outlined.	https://www.nature.com/articles/nbt.2696	October 2013
2	Studies of test concordance	FoundationOne CDx Technical Information	Concordance studies between the FoundationOne CDx assay and other companion diagnostic tests used to identify NSCLC patients suitable for treatment were performed as part of obtaining FDA-approval of FoundationOne CDx. A high degree of concordance was reported across all comparisons.	https://assets.ctfassets.net/vhribv12lmne/6Rt6csmCPuaguuqmgi2iY8/e3a9b0456ed71a55d2e4480374695d95/FoundationOne_CDx.pdf	December 2017
3	Studies of test concordance	Comparison of Next Generation Sequencing, Quantitative PCR, and Sanger Sequencing for Mutation Profiling of EGFR, KRAS, PIK3CA and BRAF in Clinical Lung Tumors (Gao et al. 2016)	138 NSCLC sample were examined for mutations in EFR, KRAS, PIk3CA and BRAF genes using NGS, QPRC and Sanger Sequencing. Sanger Sequencing failed to detect variants with rates lower than 15%. Similar sensitivity, specificity and high concordance was reported between NGS and QPCR.	https://www.clin-lab-publications.com/article/2109	2016
4	Clinical utility study	Broad, hybrid capture-based next generation sequencing identifies actionable genomic alterations in "driver-negative" lung adenocarcinomas: (Drilon et al. 2015)	FoundationOne was used to perform CGP on 31 cases of NSCLC with no evidence of a clinically actionable genomic alteration with 'standard' assays (including FISH). A genomic alteration with a corresponding targeted therapy currently available was found in 8/31 (26%) of cases. Of these 8 cases, 6 patients (75%) went on to receive targeted therapy based on the results of CGP.	http://clincancerres.aacrjournals.org/content/early/2015/01/07/1078-0432.CCR-14-2683.short	January 2017

	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**
5	Clinical utility study	Clinical framework for next generation sequencing based analysis of treatment predictive mutations and multiplexed gene fusion detection in non-small cell lung cancer (Lindquist et al. 2017)	533 consecutive NSCLC cases were tested using NGS (Illumina TruSight Tumor Assay). 15.3% of patients with adenocarcinoma were found to harbour an EGFR/ALK mutation suitable for targeted therapy with a further 10.6% (50.3% if including KRAS) of patients eligible for emerging targeted treatments.	http://www.oncotarget.com/index.php?journal=oncotarget&page=article&op=view&path[]=16276&pubmed-linkout=1	March 2017
6	Clinical utility study	Comprehensive genomic profiling identifies a subset of crizotinib responsive ALK-rearranged non-small cell lung cancer not detected by fluorescence in situ hybridization: (Ali et al. 2016)	FoundationOne was used to perform CGP on 1,070 cases of NSCLC. A total of 47 (4.4%) of patients were found to harbour ALK rearrangement. 41/47 (87%) had an EML4-ALK fusion. Of 41 patients harbouring EML4-ALK fusion, 31 had prior FISH testing results available. Of these, 20 were ALK FISH positive, and 11 (35%) were ALK FISH negative. Of the latter 11 patients, 9 received crizotinib based on the CGP results, and 7 achieved a response with median duration of 17 months.	http://theoncologist.alphamedpress.org/content/21/6/762.short	May 2016
7	Clinical utility study	Comprehensive Genomic Profiling Identifies Frequent Drug-Sensitive EGFR Exon 19 Deletions in NSCLC not Identified by Prior Molecular Testing: (Schrock et al. 2016)	The EGFR mutation profile of 400 consecutive cases of NSCLC patients harbouring EGFR Δex19 alterations was assessed using FoundationOne. Pathology reports of a subset of 250 cases were also reviewed, with EGFR test results from an alternate testing method available for 71 cases. In 12/71 (17%) of these cases EGFR alterations were identified with FoundationOne® that had previously tested negative for EGFR.	http://clincancerres.aacrjournals.org/content/22/13/3281	July 2016
8	Non-randomised trial	Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small cell lung cancer: an open-label, phase 2 trial (Planchard et al. 2017)	In this trial patients with BRAF V600E mutation positive NSCLC were treated with dabrafenib+trametinib. Based on the duration of response data reported in this trial, TGA-approval of dabrafenib+trametinib in BRAF V600E NSCLC patients was obtained in 2019.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30679-4/fulltext	July 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***
9	Phase 3 Randomised controlled trial	Osimertinib in Untreated EGFR-Mutated Advanced Non-Small Cell Lung Cancer: (Soria et al. 2018)	This Phase 3 study assessed the efficacy and safety of osimertinib (80 mg orally, once daily) versus a standard of care EGFR TKI (either gefitinib [250 mg orally, once daily] or erlotinib [150 mg orally, once daily]) in patients with locally advanced or metastatic NSCLC that is known to be EGFR sensitising mutation (EGFRm) positive, treatment naïve and eligible for first-line treatment with an EGFR TKI. Improved median duration of response and 18-months overall survival rate was reported in patients treated with osimertinib compared with gefitinib/erlotinib. Patients are still being monitored for long-term overall survival.	https://www.nejm.org/doi/full/10.1056/nejmoa1713137	January 2018
10	Non-randomised trial	Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children (Drilon et al. 2018)	This Phase 1-2 trial is assessing larotrectinib in solid tumours harbouring a gene rearrangement in NTRK1/2/3. This trial assessed NSCLC patients in a separate arm to other tumour types. Based on the interim results of this study larotrectinib has received FDA-approval as a 'tumour agnostic' treatment for patients harbouring a gene rearrangement in NTRK1/2/3.	https://www.nejm.org/doi/full/10.1056/nejmoa1714448	February 2018
11	Non-randomised trial	Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3, ROS1, or ALK Gene Rearrangements (Fusions): NCT0256867	Patients with NSCLC found to harbour the following gene rearrangements were allocated to separate arms of the trial and received treatment with entrectinib: NTRK1/2/3; ROS1; ALK. The duration of PFS and OS are secondary outcomes for this trial.	https://clinicaltrials.gov/ct2/show/NCT02568267?term=NCT02568267&rank=1	Publication pending
12	Clinical Management Guidelines	NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer: (NCCN 2019)	The NCCN guidelines outlined 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. 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://www.nccn.org/professionals/default.aspx	October 2019

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

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

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.***

As outlined above, this application is seeking that NGS assays be assessed as a 'treatment agnostic' biomarker assay for NSCLC patients, i.e. the results of testing may be used to identify patients eligible to access all targeted treatments currently listed on the PBS. It is also proposed that testing could be used to identify patients suitable for treatment with future targeted therapies for NSCLC cancer listed on the PBS after review of the efficacy, safety and cost-effectiveness of the therapy by the PBAC. The details of clinical trials assessing the role of CGP and the use of targeted lung cancer therapies with a biomarker anticipated to report in the near future are outlined below.

	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.	Non-randomised 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: NCT01639508	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.	https://clinicaltrials.gov/ct2/show/NCT01639508?term=NCT01639508&rank=1	Unknown
2.	Non-randomised trial	A Study of Lorlatinib in Advanced ALK and ROS1 Rearranged Lung Cancer With CNS Metastasis in the Absence of Measurable Extracranial Lesions: NCT02927340	In this Phase 2 trial patients with NSCLC harbouring an ALK or ROS1 gene rearrangement received treatment with lorlatinib. Patients could be treatment naïve or received prior treatment on at least 1 prior ALK/ROS1 inhibitor. The duration of OS is a secondary outcome for this trial.	https://clinicaltrials.gov/ct2/show/NCT02927340?term=NCT02927340&rank=1	March 2020
3.	Non-randomised trial	ASPiRATION Lung Cancer Study	Comprehensive Genomic Profiling will be performed in 1,000 non-squamous NSCLC patients in Australia. Patients identified with an actionable mutation will have to opportunity to receive targeted therapy as part of this study. This study is scheduled to commence in July 2020.	https://altg.com.au/research-overview/clinical-trials-list/	2022

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

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

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

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

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

Organisations which may verify the clinical relevance of CGP tumour tissue from NSCLC patients in order to determine suitability for targeted treatment are:

1. The Royal College of Pathologists of Australasia (RCPA)
2. The Medical Oncology Group of Australia (MOGA)
3. The Australian Genomic Cancer Medicine Cancer Medicine Centre (AGCMC)

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

There is currently no MBS reimbursed CGP service for NSCLC patients in Australia, however NGS assays are currently being used in academic centres and some private pathology laboratories.

The Applicant understands that some small NGS panels are routinely used in clinical practice and claimed under the single gene MBS items (e.g. MBS item7337 for EGFR testing).

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

The Lung Foundation of Australia

The Lung Foundation previously provided support for a submission from Roche Products for Foundation Medicine (letter dated 4 July 2018).

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:

- 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)
- 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)

The current Australian regulatory status for NGS oncology assays are as RUO products. Under the Australian regulatory framework for IVDs, local laboratories may use RUO NGS assays as in-house IVDs after the conduct of appropriate testing and validation.

The FoundationOne® CDx assay is FDA approved as an IVD companion diagnostic in solid tumours (including NSCLC). As outlined previously, Foundation Medicine and Roche Sequencing Solutions (Roche Diagnostics) are developing a CGP panel based on the FoundationOne® CDx assay that will enable laboratories to perform CGP locally.

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

The following two experts have had the most experience using Foundation Medicine CGP service in Australia:

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**

Name of expert 3: **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), INDICATION, 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:

Based on projections of lung cancer incidence outlined in the background document to the PD-(L)1 checkpoint inhibitor stakeholder meeting (DoH 2019) there will be 12,990 new cases of lung cancer in Australia in 2020. Non-small cell lung cancer is a subtype of lung cancer that accounts for around 86.6% of lung cancers. Based on 86.6% of lung cancers being classified as NSCLC there was an estimated 11,249 incident cases of NSCLC in Australia in 2020, of which 8,696 (77.3%) were Stage III or IV (DoH 2019).

Patients with advanced lung cancer have a poor prognosis. For patients with NSCLC the 5-year survival rates for patients with Stage III or Stage IV disease is 36%-13% (Stage IIIA-Stage IIIC) and 10% respectively[3]. Resulting from the low 5-year survival rates for patients with lung cancer, the mortality burden of lung cancer is very high. In Australia in 2018, it is estimated that there were 8,898 lung cancer-related deaths (AIHW 2019).

NSCLC is a heterogeneous disease with a wide diversity of genomic subtypes known to drive cancer cell growth. This has led to the development and introduction into clinical practice of several therapies targeting these oncogenic drivers, e.g. EGFR, ALK, and ROS1-targeting tyrosine kinase inhibitors (TKIs). There are additional therapies targeting new oncogenic drivers under active clinical development or in the regulatory assessment process, including agents targeting patients harbouring genomic aberrations in BRAF, RET, NTRK, MET and HER2 genes.

Increasingly the selection of the most appropriate treatment for NSCLC patients is informed by the results of molecular testing. As such, there is a need for equitable access to testing with an assay that robustly and reliably assesses the presence of genomic alterations in tumour tissue to inform appropriate treatment selection.

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:

NSCLC patients would have CGP performed using a NGS assay prior to treatment initiation. Based on current clinical management guidelines and PBS restrictions for systemic lung cancer treatments, it is reasonable that patients with Stage IIIB (locally advanced) or Stage IV (metastatic) disease of non-squamous (or not otherwise specified) histology would be considered for CGP.

Disease staging and histology assessment is part of the routine management of lung cancer patients. Therefore, there would be no changes in the use of investigative procedures used during initial disease staging if CGP using a NGS assay was used to identify genomic alterations used to inform decisions to use a targeted treatment.

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):

Guidelines for the management of NSCLC (Planchard et al. 2018, NCCN 2019) outline the following procedures as part of the diagnosis and initial assessment of NSCLC patients: physical examination and assessment of medical history; complete blood count; renal and liver function testing; pathologic evaluation of tumour biopsy specimen to determine histological subtype; contrast-enhanced computed tomography

[3] https://www.cancer.org/cancer/non-small-cell-lung-cancer/detection-diagnosis-staging/survival-rates.html

(CT) scan of the chest and upper abdomen; and a potential further FDG-PET scan if the presence of metastatic disease is suspected after CT scan (equivocal CT scan result). These investigations should be performed on all patients as part of the initial diagnosis and staging of disease.

Based on initial diagnosis and staging outcomes, if the patient has locally advanced or metastatic disease unsuitable for conservative management or surgical resection, the use of systemic treatment is recommended.

Prior to the commencement of systemic therapy for locally advanced or metastatic NSCLC, molecular testing of the patient's tumour tissue should be undertaken to determine eligibility to PBS-listed treatment with EGFR-TKIs (gefitinib, erlotinib, afatinib), ALK-TKIs (crizotinib, ceritinib, alectinib) or ROS1-TKIs (crizotinib). Due to simultaneous assessment all genomic alterations currently used to determine patient eligibility to access target treatment through the PBS, it is proposed that CGP using a NGS assay would be used as an alternative to a sequence of individual EGFR, ALK and ROS1 biomarker testing currently listed on the MBS.

PART 6b – INFORMATION ABOUT THE INTERVENTION

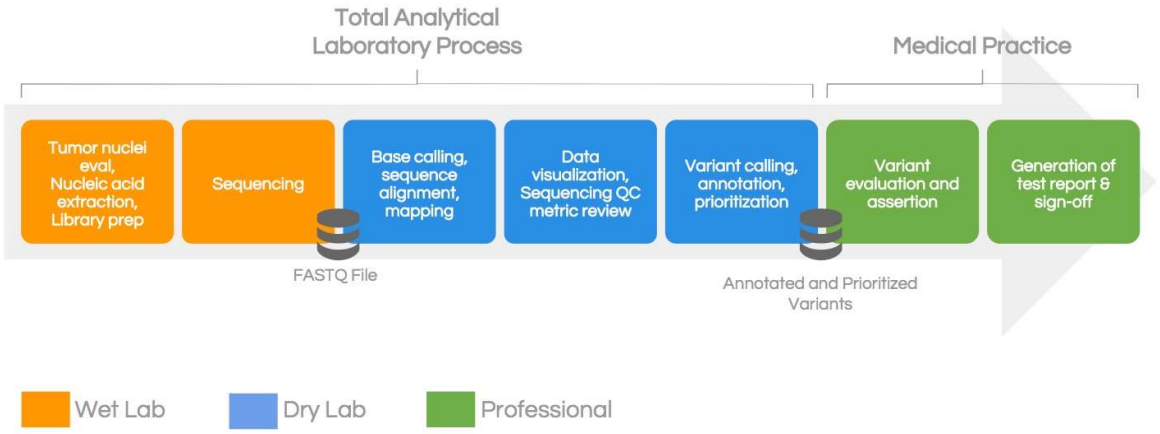
27. Describe the key components and clinical steps involved in delivering the proposed medical service:

The conduct of CGP using a NGS assay involves the following key steps:

- Isolation of tumour DNA from tumour tissue specimen
- Preparation of sequencing libraries
- Enrichment of sequencing libraries for genes of interest
- Sequencing of enriched libraries
- Analysis and reporting of test results

A general overview of the workflow associated with the conduct of CGP using NGS assays is provided in Figure 1.

Figure 1 Workflow applicable to NGS assays



Source: https://www.pieriandx.com/news-room/cap-distributive-model-of-ngs-testing

Wet lab and dry lab components of the workflow associated with CGP using NGS assays can be performed on multiple tumour specimens at the same time. Thus, some of the laboratory components of CGP using NGS assays benefit from efficiencies from 'batch processing' and/or automation of processing clinical samples. In contrast, the curation of variants detected in a tumour specimen and preparation of a test report outlining the results of biomarker testing must be performed manually and on a per patient basis. Thus, the curation and reporting to CGP test results represents a significant investment of time and expertise and will contribute to an increase in the cost of NGS based testing compared with single gene testing currently funded through the MBS.

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

Not applicable.

While there is a degree of variation as to the unique list of genes assessed with various NGS assays this application does not proposed to limit the use of CGP to a specific NGS assay with a registered trademark(s).

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

Not applicable.

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

It is proposed that CGP of tumour tissue using a NGS assay would be performed once per course of therapy. For most NSCLC patients testing for genomic alterations will be performed when a decision to initiate systemic treatment is made.

In some cases testing of NSCLC tumour tissue for genomic alterations may be requested in patients diagnosed with early-stage disease (not amenable to management with systemic therapy) to avoid delays, costs and safety issues associated with the collection of a second biopsy specimen at the time of disease progression. In this situation it is proposed that the results of testing conducted at the time of diagnosis would be used to inform treatment decisions at the time of initiation with systemic therapy.

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:

No additional healthcare resources are required when CGP is performed using a NGS assay.

The handling of NSCLC tumour samples in pathology laboratories is required as part of the preparation of a tumour tissue specimen for histological review during disease staging and tissue archiving purposes.

All tests for genomic alterations currently funded on the MBS for NSCLC patients have the potential to be consolidated with the use of a single NGS assay. Subsequently, there is likely to be a <u>reduction</u> in the number of individual testing procedures performed as part of the diagnostic work-up of NSCLC patients if CGP is undertaken using these 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.

All steps associated with the conduct of CGP using a NGS assay will be performed by a local pathologist/laboratory technician on the request of the treating clinician, with results of testing being reported back to the treating clinician to guide treatment selection.

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

The conduct of CGP using a NGS assay could be delegated to a laboratory within the pathology laboratory network with the expertise, capital equipment and National Association of Testing Authorities, Australia (NATA) accreditation required to perform NGS-based gene panel testing.

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

Not applicable.

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:

The conduct of testing for genomic alterations in tumour tissue from NSCLC patients and use of targeted treatment is already established in Australian clinical practice. As such, no additional formal training or

qualifications would be required with availability of CGP using a NGS assay. It is also noted that testing for genomic alterations using NGS is already being undertaken in several public hospital laboratories and private pathology laboratory networks, supporting the position that additional training of qualifications are not required prior to CGP of NSCLC tumour specimens using NGS assays being delivered in Australia.

All laboratories performing genomic testing used to inform patient management using a NGS assay must hold the appropriate accreditations to do so. Testing must be performed in line with the standards set out in the 'Requirements for human medical genome testing utilising massively parallel sequencing technologies' document (NPACC 2017).

Audits against the testing standards and laboratory accreditation is undertaken by NATA.

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

- ☒ Inpatient private hospital
- ☒ Inpatient public hospital
- ☐ Outpatient clinic
- ☐ Emergency Department
- ☒ Consulting rooms
- ☒ Day surgery centre
- ☐ 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:

Physical examinations and ongoing assessments of NSCLC patients would be most likely to take place in the consulting rooms of the patients' managing clinician.

The collection of the tumour tissue used for testing may occur as part of an admitted episode of hospital care (private or public hospital) or in a day surgery centre.

Conduct of CGP using a NGS assay would take place in a NATA accredited laboratory.

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 comparators nominated for NGS assays are all molecular biomarker tests currently listed on the MBS and used to identify NSCLC patients eligible for treatment with a targeted therapy, specifically:

- Testing of EGFR gene mutation status
- Immunohistochemistry testing as triage ALK testing
- Testing of ALK gene rearrangement status by FISH
- Immunohistochemistry testing as triage ROS1 testing
- Testing of ROS1 gene rearrangement status by FISH

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

☒ Yes (please provide all relevant MBS item numbers below)
☐ No

Testing of EGFR gene mutation status: MBS item 73337

Immunohistochemistry testing as triage ALK and ROS1 testing: eligible under MBS item 72846

Testing of ALK gene rearrangement status by FISH: MBS item 73341.

Testing of ROS1 gene rearrangement status by FISH: MBS item 73344.

40. Define and summarise the current clinical management pathways 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):

As per the current access arrangements to PBS-listed targeted lung cancer treatments the following treatments may be used based on the results of CGP with a NGS assay (or testing using molecular biomarker tests currently listed on the MBS):

- EGFR mutation positive: erlotinib; gefitinib; afatinib; osimertinib
- ALK gene rearrangement positive: alectinib; ceritinib; crizotinib; brigatinib (PBAC recommended November 2019)
- ROS1 gene rearrangement positive: crizotinib; entrectinib (pending outcome of PBAC decision at March 2019 meeting)

Pending the outcome of the clinical development of targeted lung cancer treatments the following new treatments may be used based on the results of CGP with a NGS assay in the foreseeable future, noting that use of these treatments in lung cancer patients will be contingent on obtaining TGA-approval and PBS listing as per standard processes:

- EGFR Ex19del, L858R: dacomitinib
- BRAF V600E positive: dabrafenib+trametinib
- ROS1 gene rearrangement positive: lorlatinib; cabozantinib; repotrectinib
- RET gene rearrangement positive: cabozantinib; vandetanib
- NTRK gene rearrangement positive: entrectinib; larotrectinib
- MET amplification: cabozantinib
- HER2 mutation positive: ado-trastuzumab emtansine

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

☒ Yes (instead of nominated comparators)
☐ No

(b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:

It is anticipated that CGP using a NGS assay will largely substitute the use of EGFR, ALK (IHC triage and FISH) and ROS1 (IHC triage and FISH) testing in NSCLC patients to determine eligibility to access PBS-listed targeted treatment. That is, there will be no need to mandate the confirmation of the biomarker status reported with a NGS assay with an alternate methodology currently funded through the MBS.

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):

The use of CGP using a NGS assay proposed in this application is as an alternative to molecular biomarker tests currently used to determine eligibility for lung cancer patients to access PBS-listed targeted treatments. Therefore, no change to the clinical management pathway for NSCLC patients beyond the treatment decisions informed by the results of molecular biomarker testing for NSCLC patients already listed on the MBS is expected.

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):

It is foreshadowed that the evidence presented in the Applicant Developed Assessment Report will support a claim that CGP using a NGS assay is at least as effective, and conceivably more effective, in identifying genomic alterations used to inform clinical management decisions for lung cancer patients compared with the sequential use of molecular biomarker tests currently listed on the MBS.

Studies have shown that patients previously assessed as being EGFR or ALK negative by alternate testing methodologies were subsequently found to harbour EGFR gene mutations (Schrock et al. 2016) or ALK gene rearrangements (Ali et al. 2016, Lin et al. 2019) using CGP with a NGS assay. On this basis, it is conceivable that CGP using a NGS assay is more effective in identifying patients suitable for treatment with a targeted therapy than the molecular biomarker testing methodologies currently funded through the MBS.

An advantage of NGS assays is that they are able to simultaneously assess all molecular biomarkers used in the diagnostic work-up of NSCLC patients currently listed on the MBS in a single test as opposed to current practice where each test must be performed in a sequence in order to be eligible to attract a Medicare benefit. As such, it is foreshadowed that a claim that CGP using NGS assays have at least a non-inferior, and potentially superior safety profile compared with biomarker tests currently on the MBS will be presented in the Applicant Developed Assessment Report. The potentially superior safety profile would arise from a reduction in re-biopsy procedures required to undertake all of the biomarker tests recommended for NSCLC patients should the original tumour tissue specimen is insufficient or becomes depleted with the follow-on associated reduction in risk of complications associated with a lung biopsy.

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

☒ Superiority	Potential for superior safety resulting from a reduction in re-biopsy procedures
☒ Non-inferiority	Non-inferior, and conceivably superior, in identifying genomic alterations

Note that these claims relate to those foreshadowed to be supported by the evidence presented in an Applicant Developed Assessment Report reviewing the efficacy and safety of CGP using NGS assays compared with the sequential use of molecular biomarker tests currently listed on the MBS. This document is not making a clinical claim for any specific NGS assay offered by a commercial manufacturers which does not have the regulatory approval as an IVD companion diagnostic.

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: As the collection of tumour tissue is already required as part of the diagnostic work-up of lung cancer patients there are no additional safety considerations associated with the conduct of CGP using NGS assays.

Clinical Effectiveness Outcomes: The intended use of CGP using a NGS assay sought through this MSAC application is as an alternative to molecular biomarker tests currently listed on the MBS used to identify NSCLC patients suitable for treatment with a targeted therapy listed on the PBS.

The outcomes relevant to the assessment of the efficacy of NGS assays for the use proposed in this MSAC application are:

- Measures of analytical sensitivity and specificity

- Results of concordance studies between NGS assays and comparator biomarker assays (EGFR gene mutation testing; ALK FISH testing; ROS1 FISH testing)

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

As previously outlined, there will be an estimated 12,990 new cases of lung cancer in Australia in 2020. Non-small cell lung cancer is a subtype of lung cancer that accounts for around 86.6% of lung cancers worldwide. Based on a rate of 86.6% of lung cancers being classified as NSCLC there will be an estimated 11,249 incident cases of NSCLC in Australia in 2020, of which 8,696 (77.3%) were Stage III or IV (DoH 2019).

Not all patients with locally advanced or metastatic NSCLC would have a performance status score consistent with being eligible for treatment through the PBS, and not all patients will opt to commence treatment. Based on assumptions previously accepted by the PBAC and outlined in the background document to the PD-(L)1 checkpoint inhibitor stakeholder meeting provided to Roche, 63.3% of NSCLC patients have an ECOG performance score of 0 or 1 and are eligible for PBS-listed treatment and 85% of patients opt for treatment. Thus, in 2020 it is estimated that there would have been 4,679 (8,374*63.3%*85%) incident cases of NSCLC considered for systemic treatment.

An assessment of the mortality-to-incidence ratio (MIR) for lung cancer was conducted based on the number of incident cases and deaths reported for lung cancer in Australia between 2015-2017 using data reported in (AIHW 2019).

Year	2015	2016	2017
Incidence	11,788	11,929	12,209
Mortality	8,416	8,410	8,717
MIR	0.71	0.71	0.71

The MIR for lung cancer reported in Australia between 2015-2017 (0.71) is relatively close to 1, indicative of lung cancer patients having a short average survival. Based on the assessment of MIR, and the very low 5-year survival rate for patients with locally advanced or metastatic disease, it is reasonable to conclude that there is not a large pool of prevalent patients with NSCLC who would be considered for CGP using a NGS assay.

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

The assessment of molecular biomarkers in NSCLC patients is most applicable at the time of initiating systemic treatment. Clinical management guidelines recommend that patients found to harbour a genomic alteration be managed with a corresponding targeted treatment as a first-line treatment (Planchard et al. 2018, NCCN 2019). Therefore, it is reasonable to conclude that the majority of patients would undergo CGP using a NGS assay once throughout their management for locally advanced/metastatic (Stage IIIB/IV) disease.

The Applicant acknowledges the presence of the T790M mutation must be determined in order to determine eligibility to access osimertinib as a second-line therapy in patients with NSCLC through the PBS. In this context, a repeat assessment of EGFR gene mutation status would be conducted on tumour tissue collected upon disease progression with first-line EGFR TKI treatment (gefitinib, erlotinib, afatinib). The repeat EGFR testing to assess the presence of the T790M mutation is facilitated through MBS item 73351 and would not necessitate repeat CGP.

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

The identification of NSCLC patients with locally advanced or metastatic disease (Stage IIIB/IV) suitable for treatment with a targeted therapy as first-line treatment is required prior to a patient commencing treatment. As such, the use of CGP using a NGS based assay would be for less than one year.

As outlined above, monitoring of treatment response by CGP using a NGS assay may be recommended as part of standard clinical management in the future. If this was the case then it is likely that testing would be performed over a timeframe beyond one year. However, the role of CGP using a NGS assay is an area of ongoing research and is outside the scope of the assessment sought in this MSAC Application Form.

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

Epidermal growth factor receptor testing is the initial molecular biomarker test used in the testing sequence of MBS-listed tests used in NSCLC patients. Therefore, the number of EGFR tests (MBS item 73337) processed through the MBS for the 2019 calendar year of 4,603 represents a reasonable maximum estimate of the number of patients who may utilise CGP with a NGS assay in the first full year.

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 number of NSCLC patients opting for treatment outlined in the background document to the PD-(L)1 checkpoint inhibitor stakeholder meeting from 2019-2023 and the number of EGFR tests funded through the MBS in 2019 were used to estimate the maximum uptake of CGP using a NGS assay over the next 3 years (see below).

Year	2019	2020	2021	2022	2023
NSCLC patients eligible for PBS-listed treatment	4,592	4,679	4,765	4,852	4,938
# EGFR Test Processed through MBS	4,603	-	-		
% of incident patient tested	100%	100%	100%	100%	100%
Maximum uptake of CGP using a NGS assay	4,603	4,679	4,765	4,852	4,938

The MBS item descriptor proposed for CGP using a NGS assay includes several criteria to address the potential for 'leakage' in the use of testing beyond the patient population proposed in this application. Most notably it is proposed that CGP funded through the MBS would be restricted to patients with lung cancer being considered for treatment with a systematic therapy that is available through the PBS. This ensures that the use of CGP using a NGS assay would be consistent with the use of molecular biomarker tests currently listed on the MBS and used to identify NSCLC patients eligible for treatment with a targeted therapy.

PART 8 – COST INFORMATION

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

The Applicant is aware of its requirement to provide a cost for CGP using a NGS assay, and associated assessment of budget impact, and commits to doing so as part of the preparation of the Applicant Developed Assessment Report for consideration by MSAC.

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

The optimal turnaround time between the receipt of a patient tumour tissue specimen at the pathology laboratory and availability of results is 5 days, however typical turnaround times are believed to be 10-12 days.

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

Category 6 – Pathology Services

Comprehensive genomic profiling using a next generation sequencing assay performed on tumour tissue from a patient diagnosed lung cancer, requested by, or on behalf of, a specialist or consulting physician, to determine if the eligibility requirements to access targeted treatment under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Indications, biomarkers and therapies eligible to access comprehensive genomic profiling using a next generation sequencing assay under the Medicare Benefit Schedule (MBS) are:

Indication	Biomarker	Treatment
Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer. Patient must have non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified.	Epidermal growth factor receptor (EGFR) gene	erlotinib; gefitinib; afatinib
Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer. Patient must have non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified.	Anaplastic lymphoma kinase (ALK) gene rearrangement	crizotinib; ceritinib; alectinib;
Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer. Patient must have non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified.	c-ROS proto-oncogene 1 (ROS1) gene rearrangement	crizotinib

Fee: To be confirmed

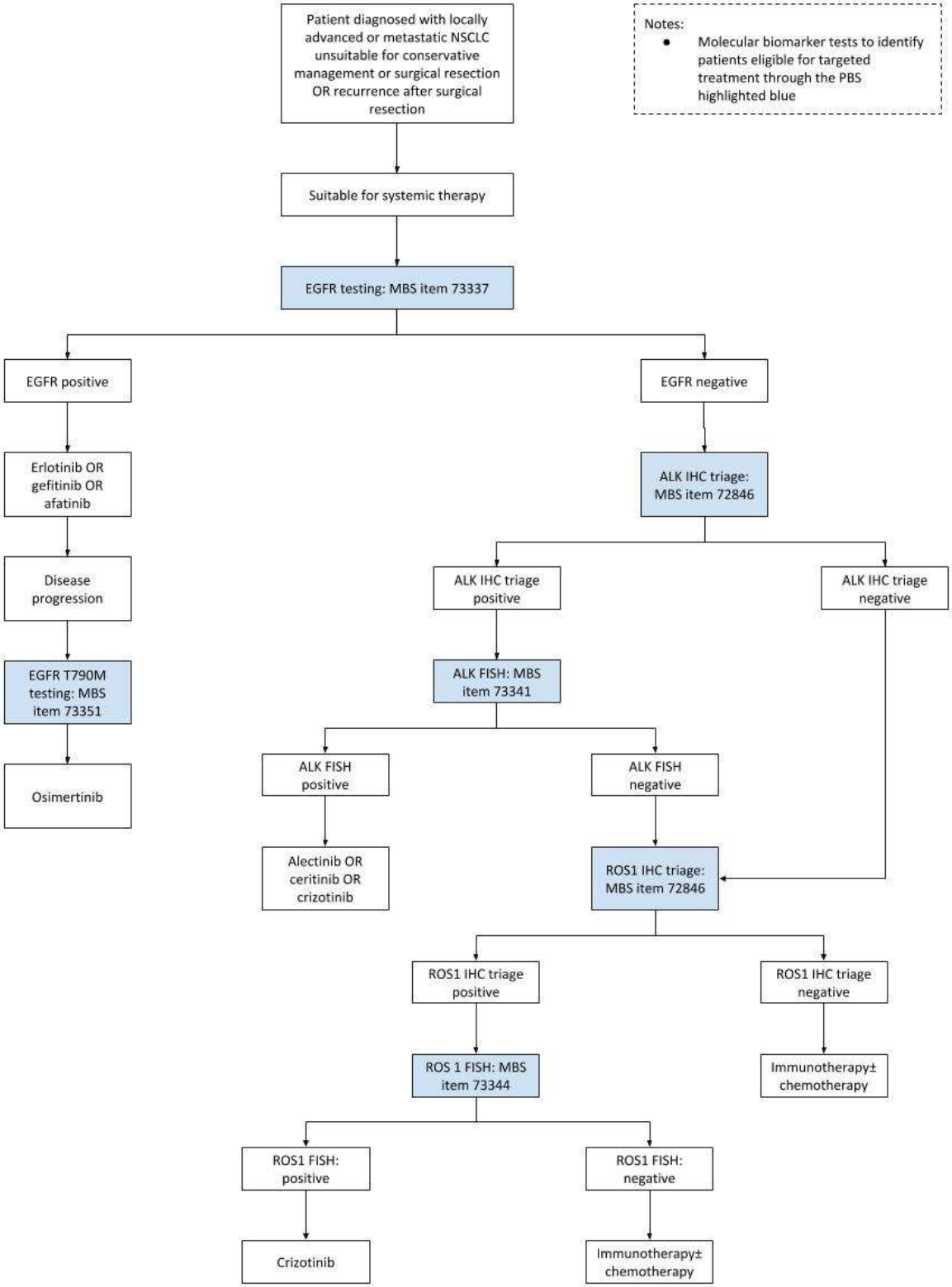
It is envisaged that the sponsors of targeted therapies under clinical development can update the MBS item descriptor proposed above to reflect the introduction of additional indications, biomarkers or treatments through the streamlined co-dependent technology reimbursement pathway by:

- Lodging a major submission to the PBAC presenting evidence of the efficacy, safety, and cost-effectiveness of the targeted lung cancer therapy, and
- Lodging a submission to MSAC requesting an amendment to the MBS item for CGP of lung cancer tumour tissue specimens using a NGS assay to include reference to any new indication, biomarker or treatment.

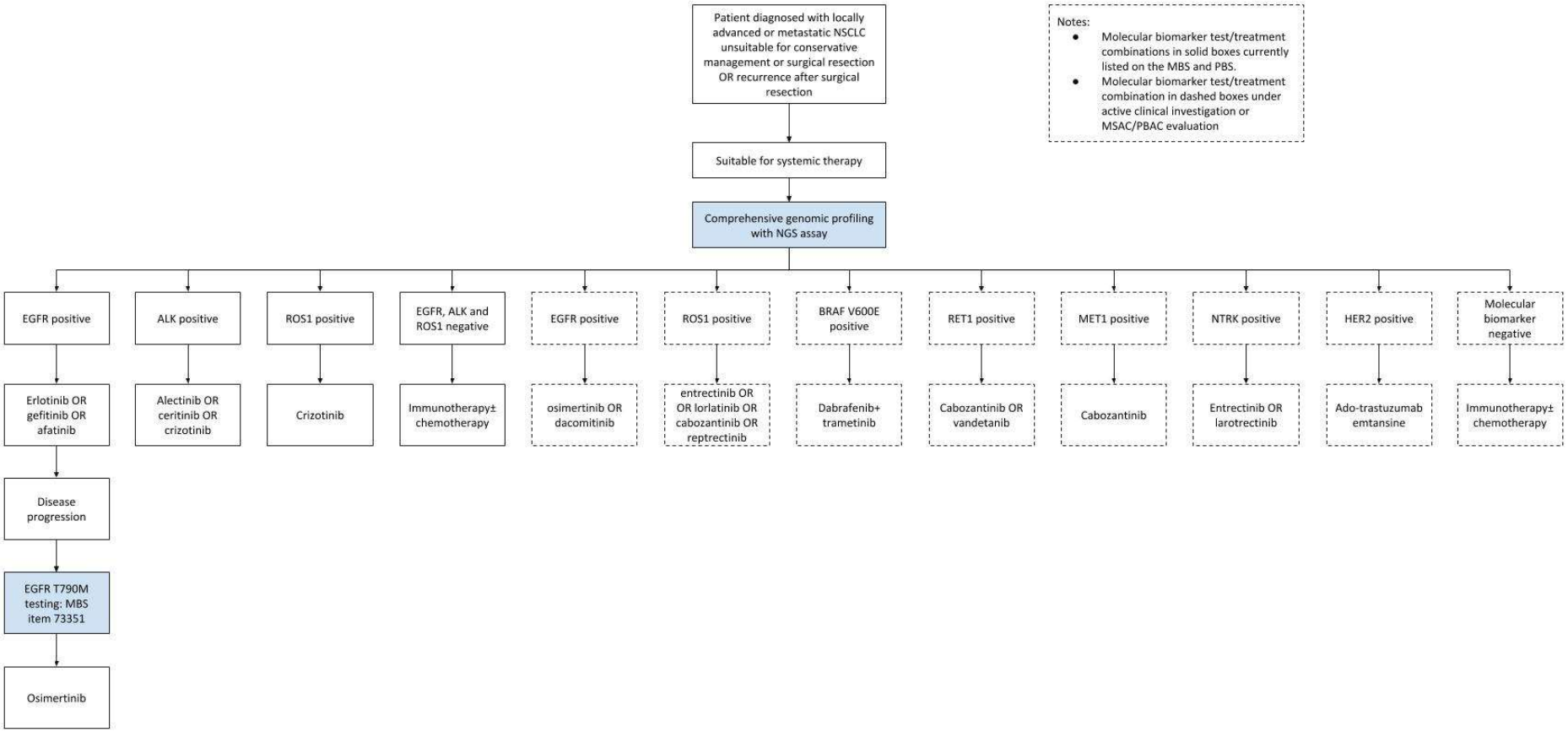
This proposal has the potential to substantially reduce the resource requirements associated with the MSAC assessment of future biomarkers used in lung cancers. Further, there is potential to reduce the time to listing for new lung cancer treatments on the PBS and that will benefit patients, the Department of Health and sponsors of targeted treatments for lung cancer alike.

Attachments

A flowchart representing the current sequencing of molecular biomarker testing to determine NSCLC patient eligibility to access targeted lung cancer treatments on the PBS is provided below (effective March 2020).



A flowchart representing the use of CGP using a NGS assay to perform molecular biomarker testing to determine NSCLC patient eligibility to access targeted lung cancer treatments on the PBS is provided below.



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