Australian Government

Department of Health

Application Form

(New and Amended

Requests for Public Funding)

(Version 2.4)

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):
Corporation name: **The Royal College of Pathologists of Australasia (RCPA)**
ABN: **Redacted**
Business trading name: **Redacted**

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

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Somatic Tumour Gene Panel Test

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)

The medical conditions relevant to the proposed service include all malignancies for which a somatic tumour gene panel test assists with determining suitability for therapy.

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 somatic tumour gene panel testing to detect genomic alterations in tumours to determine therapy suitability and identification of changes associated with resistance to therapy.

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

☒ Yes
☐ No

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

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

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

N/A

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

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):

Insert description of 'other' amendment here

(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:

N/A

7. What is the type of service:

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

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

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):

PBS drug	PBS item numbers									
dabrafenib	02846T	02954L	02963Y	10003L						
erlotinib	10014C	10019H	10020J	10022L	10025P	10028T				
gefitinib	08769M									
cetuximab	04312Y	04435K	04436L	04731B	07223E	07240C	07242E	07273T	10262D	10265G
panitumumab	10069Y	10082P	10508C	10513H						
crizotinib	10322G	10323H								
ceritinib	11056X									

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

N/A

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

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

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

☐ Yes
☒ No

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

N/A

Billing code(s): Insert billing code(s) here
Trade name of prostheses: Insert trade name here
Clinical name of prostheses: Insert clinical name here
Other device components delivered as part of the service: Insert description of device components here

(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):

Insert sponsor and/or manufacturer name(s) here

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

Single use consumables:

Several assays are available for somatic tumour gene panel tests and all require single use consumables such as laboratory pipette tips.

This application does not endorse any one specific commercial product. A detailed listing of all products and their consumables is beyond the scope of this application. It should be noted that new products will continue to be developed using the same scientific principles.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

Type of therapeutic good: In-vitro diagnostic test
Manufacturer's name: Various
Sponsor's name: Not applicable

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

☒ Class III
☐ AIMD
☐ N/A

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

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

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

☒ Yes (if yes, please provide details below)
☐ No

ARTG listing, registration or inclusion number:

ARTG licence numbers for Acquired genetic alteration IVDs including but not limited to:

AA-Med Pty Ltd 214482
Abacus ALS Pty Ltd 255352 256572 262298
Abbott Australasia Pty Ltd Molecular Division 196286
Biomerieux Australia Pty Ltd 217781
Bio-Strategy Pty Ltd 226487
Carl Zeiss Pty Ltd 266568
Cepheid Holdings Pty Ltd 226631
Dako Australia Pty Ltd 199420 264573
Diagnostic Solutions Pty Ltd 201693
Diagnostic Technology Pty Ltd 217262
Elitechgroup Australia Pty Ltd 278596
Emergo Asia Pacific Pty Ltd 262500
ESL Biosciences Australia 2102 Pty Ltd 214427
Illumina Incorporated 276134
In Vitro Technologies Pty Ltd 225995
Key Diagnostics Pty Ltd 270292
Leica Microsystems Pty Ltd 191254
PerkinElmer 233472
Qiagen Pty Ltd 214994 226453 238792
Roche Diagnostics Australia Pty Limited 180933 192394 192395 194319 196363
Thermo Fisher Scientific Australia Pty Ltd 227503 256113
Vela Diagnostics Australia Pty Ltd 228024 235394

TGA approved indication(s), if applicable:
TGA approved purpose(s), if applicable:

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?

N/A

☐ Yes (please provide details below)
☐ No

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

N/A

☐ Yes (please provide details below)
☐ No

PART 4 – SUMMARY OF EVIDENCE

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

	Type of study design*	Title of journal article or research project (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.	Health economics study	Sabatini LM, Mathews C, Ptak D, et al: Genomic Sequencing Procedure Microcosting Analysis and Health Economic Cost-Impact Analysis: A Report of the Association for Molecular Pathology. J of Mol Diagn 2016;18:319-328	US Study by Association for Molecular Pathology on cost and value analysis of specific genomic sequencing procedures (GSPs) gathered from representative laboratories' data. Cost-impact models for three clinical scenarios were generated -advanced non–small-cell lung cancer sensorineural hearing loss, and paediatric neurodevelopmental disorders of unknown genetic aetiology.	Genomic Sequencing Procedure Microcosting Analysis and Health Economic Cost-Impact Analysis: A Report of the Association for Molecular Pathology	May 2016
2.	Observational study	Salto-Tellez, M. and D. Gonzalez de Castro, Next-generation sequencing: a change of paradigm in molecular diagnostic validation. The J Path, 2014; 234(1): p. 5-10.	Review of issues to be considered in the implementation of Next-Generation Sequencing (NGS) including validation, diagnostic accuracy and cost-effectiveness.	Next-generation sequencing: a change of paradigm in molecular	2014
3.	Study of diagnostic accuracy	Tran B, Brown AM, Bedard PL, Winquist E, Goss GD, Hotte SJ, et al. Feasibility	Study of three feasibility of incorporating genomic profiling into patient management (50 patients from four	Feasibility of real time next generation sequencing of cancer genes linked to drug response: results	2013

		of real time next generation sequencing of cancer genes linked to drug response: results from a clinical trial. Int J Cancer 2013;132(7):1547-55.	**cancer centres). Samples analysed using three technologies: targeted exon sequencing using Pacific Biosciences PacBio RS, multiplex somatic mutation genotyping using Sequenom MassARRAY and Sanger sequencing. Nineteen actionable mutations were identified in 16 (32%) patients. Across technologies, results were in agreement in 100% of biopsy specimens and 95% of archival specimens. The study demonstrated that the use of next generation sequencing for real-time genomic profiling in advanced cancer patients is feasible.**	**from a clinical trial**	
4.	**Clinical practice review**	**Harris G, O'Toole S, George P, et al: Massive Parallel Sequencing of Solid Tumours - Challenges and Opportunities for Pathologists. Histopathology, online Aug 2016 ahead of publication, doi: 10.1111/his.13067.**	**Review of the role of Massive Parallel Sequencing (MPS, also referred to as Next Generation Sequencing NGS). to identify mutations/ variants and tissue RNA expression profiles for diagnosis, prognostication and targeted therapy stratification.**	**Massive parallel sequencing of solid tumours – challenges and opportunities for pathologists**	**Aug 2016**
5.	**Study of diagnostic accuracy**	**Jeck, W.R., et al., Targeted next generation sequencing identifies clinically actionable mutations in patients with melanoma. Pigment Cell & Melanoma Research, 2014; 27(4):653-663.**	**Study of genomic analysis using NGS of 248 genes, including all those of known clinical significance in melanoma. Mutations in melanoma cell lines correlated with their sensitivity to corresponding small molecule inhibitors. Actionable mutations were found in 89% of the tumor tissues analysed, 56% of which would not be identified by standard-of-care approaches. The study demonstrated the role of targeted**	**Targeted next generation sequencing identifies clinically actionable mutations in patients with melanoma**	**2014**

			sequencing for clinical use in melanoma.		
6.	**Study of diagnostic accuracy**	**Barnet, M.B., et al., EGFR-Co-Mutated Advanced NSCLC and Response to EGFR Tyrosine Kinase Inhibitors. J Thorac Oncol, online Sep 2016 ahead of publication, 10.1016/j.jtho.2016.09.001**	**Australian study into the impact of co-mutation (double or multiple mutation), compared with a single mutation, of the EGFR gene on response to tyrosine kinase inhibitors (TKIs) in patients with metastatic non small cell lung cancer (NSCLC). The study included 62 patients; eight (12.9%) with a co-mutation. Progression-free survival (PFS) in patients with EGFR co-mutation was shorter, and response rate significantly lower, than in patients with a single mutation. The study demonstrated that data from multipanel testing identifies subgroups of patients who are likely to respond poorly to standard treatment and clarification of these subgroups may improve patient care.**	**EGFR–Co-Mutated Advanced NSCLC and Response to EGFR Tyrosine Kinase Inhibitors**	**Sep 2016**
7.	**Clinical trial**	**Hollebecque A, Massard C, De Baere T, Auger N, Lacroix L, Koubi-Pick V, et al. Molecular screening for cancer treatment optimization (MOSCATO 01): A prospective molecular triage trial—Interim results. J Clin Oncol 2013; 31, (suppl; abstr 2512).**	**Clinical trial of patients with advanced solid tumours who had failed a standard therapy. Biopsies of the patients' metastatic cancers were sequenced for 30 target genes. PFS using therapy based on the genomic alterations (GA) was compared to PFS on most recent therapy [129 patients, 111 (86%) had tumor biopsy, 52 had an actionable target (40%); 25 pts (23% of biopsied pts) treated with a targeted therapy]. The trial interim results demonstrate improved anti-tumour activity results for specific GA.**	**Molecular screening for cancer treatment optimization (MOSCATO 01): A prospective molecular triage trial—interim results**	**2013**
8.	**Cost-benefit analysis**	**Kircher SM, Mohindra N, Nimeiri H: Cost estimates and economic implications**	**US cost-benefit study of expanding RAS testing for metastatic colorectal cancer. The study concluded that the increased**	**Cost Estimates and Economic Implications of Expanded RAS Testing in Metastatic Colorectal Cancer**	**2015**

		of expanded RAS testing in metastatic colorectal cancer. Oncologist 2015; 20:14-8.	**societal cost of expanded RAS testing versus standard approved KRAS exon 2 testing was inconsequential when compared with the amount of money saved by not treating the additional 18% of patients who harbor additional RAS mutations (beyond exon 2) with anti-EGFR therapy.**		
9	**Study of diagnostic accuracy**	**Sakai K, Tsurutani J, Yamanaka T, et al: Extended RAS and BRAF Mutation Analysis Using Next-Generation Sequencing. PLoS ONE 10:e0121891, 2015**	**A study into the clinical utility of multiplex deep sequencing to detect somatic mutations in KRAS, NRAS and BRAF in colorectal cancer [100 clinical formalin-fixed paraffin embedded (FFPE) tumour specimens, 15 plasma samples]. The genetic screening assay using a next-generation sequencer was validated for the detection of clinically relevant RAS and BRAF mutations using FFPE and liquid samples.**	**Extended RAS and BRAF Mutation Analysis Using Next-Generation Sequencing**	**2015**
10.	**Clinical review**	**Kruglyak KM, Lin E, Ong FS. Next-Generation Sequencing and Applications to the Diagnosis and Treatment of Lung Cancer. Adv Exp Med Biol. 2016;890:123-36.**	**Review of NGS technology in the diagnosis and treatment of lung cancer, providing a high-level overview of the role of NGS in precision oncology and the technical challenges involved.**	**Next-Generation Sequencing and Applications to the Diagnosis and Treatment of Lung Cancer**	**2016**
11.	**Clinical guidelines**	**Sepulveda AR, Hamilton SR, Allegra CJ, et al: Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists,**	**Clinical practice guidelines recommending molecular biomarkers for best practice in the diagnosis and treatment of colorectal cancer. These guidelines highlight the importance of concurrent knowledge of the RAS and BRAF status of mCRC.**	Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology	**2017**

		Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol:JCO.2016.71.9807, 2017			

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

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

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

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.	For yet to be published research that may have results relevant to your application, insert the type of study design in this column and columns below	For yet to be published research that may have results relevant to your application, insert the title of research (including any trial identifier if relevant) in this column and columns below	For yet to be published research that may have results relevant to your application, insert a short description of research (max 50 words) in this column and columns below	For yet to be published research that may have results relevant to your application, insert a website link to this research (if available) in this column and columns below	For yet to be published research that may have results relevant to your application, insert date in this column and columns below
2.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
3.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
4.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
5.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
6.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
7.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
8.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
9.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date

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

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

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

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

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

    The Royal College of Pathologists of Australasia (the applicant)

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

    Pathology Australia, Public Pathology Australia

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

    Cancer Voices Australia, COSA, Medical Oncology Group of Australia (MOGA), Cancer Voices, Human Genetics Society of Australia

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

    N/A

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), 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:

The medical condition to be investigated in this intervention is cancer, specifically those where somatic tumour gene panel testing can assist in determining suitability for therapy.

It is well recognised that cancer is an increasing disease burden in the Australian population. The age-standardised incidence rate for all cancers combined has increased from 383 cases per 100,000 people in 1982 (the year in which national incidence data were first available) to 485 cases per 100,000 people in 2012. In 2012, there were 122,093 new cases of cancer diagnosed in Australia.[a] However, with appropriate diagnosis, treatment options for cancer continue to improve so that in 2008–12, for people newly diagnosed with cancer, there is a 67% chance of surviving five years.[b] At the end of 2010, there were 905,987 people (452,946 males and 453,041 females) diagnosed with cancer in the previous 29 years who were still alive. [b] *Source: AIHW analysis of the Australian Cancer Database.*

New targeted therapies offer hope to patients with advanced cancers for improved quality of life and longer survival rates. Identification of somatic tumour genomic alterations assists in determining the most appropriate allocation of these therapies and is dependent on the availability of accurate, reliable and clinically valid pathology tests.

Specific gene rearrangements, mutations and/or copy number changes are seen in a range of neoplasms and detection of these changes is considered best practice to determine the appropriate selection of treatment for particular cancers. A limited range of genetic tests are available with public funding through the Medical Benefit Schedule (Table 1). The proposed testing with somatic tumour gene panels can concurrently identify a wider range of pathognomonic gene changes and therefore provide more information to determine the most suitable treatment.

MBS item	Test	Cancer	Therapy
73336	BRAF V600	melanoma	dabrafenib
73337	EGFR status	non-small cell lung cancer	erlotinib or gefitinib
73338	RAS mutation	colorectal cancer	cetuximab or panitumumab
73341	ALK gene rearrangement status	non-small cell lung cancer	crizotinib or ceritinib

Table 1 MBS items for targeted therapy eligibility

The use of somatic gene panels minimises the cost of testing for multiple tumour markers and decreases the risk of treatment with inappropriate therapies. In contrast to sequential testing currently available, somatic gene panels are particularly useful on limited biopsy material to avoid repeat invasive biopsy procedures with attendant increased costs and risks to the patient. This would also minimise the need for multiple episodes of paraffin block retrieval for sequential testing rather than panel testing where one retrieval only would generally be required.

For example, use of somatic gene panels could improve the testing of lung cancer patients by including HER2 and BRAF with the currently funded ALK and EGFR in a single test and offer patients wider treatment options including triage for participation in clinical trials. In colorectal cancer patients, both RAS mutations (kRAS and nRAS) could be tested concurrently for a single fee rather than sequentially as is possible in the current MBS arrangement. It should be noted that BRAF positivity in colorectal cancer may influence choice and timing of therapy more effectively than therapies allocated on the basis of RAS mutation status alone and highlights the importance of testing for BRAF concurrently to identify

these patients with poorer prognosis (Sepulveda, 2017).

Routine use of somatic cancer panel testing has been shown in Australia to provide potentially very useful information regarding the early development of resistance in lung cancer patients with EGFR mutations and additional co-mutations (Barnet, 2016). This can allow clinicians to follow patients more closely and prompt early referral for new clinical trials or different therapeutic approaches.

Somatic gene panels would also allow for greater flexibility in pathology testing as new targeted therapies become available and reduce the burden of co-dependent MBS applications for new PBS items.

References:

1. Sepulveda AR, Hamilton SR, Allegra CJ, et al: Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol:JCO.2016.71.9807, 2017
2. Barnet, M.B., et al., EGFR-Co-Mutated Advanced NSCLC and Response to EGFR Tyrosine Kinase Inhibitors. J Thorac Oncol, online Sep 2016 ahead of publication, 10.1016/j.jtho.2016.09.001

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

Patients diagnosed with cancers on histopathological or morphological investigation of tumour material would be eligible for this service to determine suitability for an available therapy.

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

The clinical management pathway would be identical to current cancer investigation and treatment:

Patient presentation to general or specialist medical practitioner with evidence of cancer.
Patient is referred for biopsy for pathological investigation.
Diagnosis of cancer is reported.
The treating medical practitioner requests further pathological investigations on the biopsy material to identify genomic alterations to determine appropriate therapy.

See Appendix A Flowcharts

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

A test of tumour tissue from a patient diagnosed with cancer to genomic alterations in cancer cells (tumour tissue, bone marrow or blood). Testing methods include In situ hybridization (ISH), polymerase chain reaction (PCR) and next generation sequencing (NGS) methodologies among others.

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

No

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

No

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

Testing would be provided as requested by the referring medical practitioner for patients with neoplastic disease requiring further classification after initial tissue pathology or haematological investigation for determination of the suitability of therapy. Follow up testing could be provided to identify resistance to 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:

N/A

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

Testing would be provided by Approved Pathology Practitioners in line with other tests in the MBS Pathology Table.

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

N/A

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

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

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

Testing would be delivered only by Approved Pathology Practitioners in Accredited Pathology Laboratories (as defined in MBS Pathology table).

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

- ☐ Inpatient private hospital
- ☐ Inpatient public hospital
- ☐ Outpatient clinic
- ☐ Emergency Department
- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Residential aged care facility
- ☐ Patient's home
- ☒ Laboratory
- ☐ Other – please specify below

Specify further details here

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

N/A

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

- ☒ Yes
- ☐ No – please specify below

Specify further details here

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 for the proposed medical service are the current pathology test items outlined earlier for ALK, EGFR, BRAF and RAS testing. Somatic gene panel testing would be required in addition to tissue pathology and/or haematological investigations but without further health care resources for obtaining the tumour tissue (i.e. on the same specimen).

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

Specify item number/s here

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):

The clinical management pathway after the comparator is the selection of cancer therapy based on current methods.

Molecular subtypes are not identified completely for all relevant cancers and selection of therapy is made on incomplete information. Inappropriate treatment may be selection resulting in ineffective therapy or patient harm. For example BRAF testing is not available for colorectal cancers, only melanoma. BRAF positive colorectal cancers may not be best treated with therapies allocated on the basis of RAS mutation status alone and therefore results may influence the choice and timing of treatment.

Where testing is available, delays occur before testing is undertaken using the current criteria. A panel test allows for concurrent molecular testing expediting the diagnostic process.

See Appendix A Flowcharts

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

☒ Yes
☐ No

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

Somatic tumour gene panel testing would replace the current service/comparator.

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):

Pathological investigation of tumour tissue, bone marrow and blood will be extended to determine the most suitable therapy for the cancer molecular subtype.

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):

Tissue pathology (H&E and IHC) and standard haematology testing often require additional molecular testing for the determination of suitability for therapy. Currently, there are limited MBS items for the comparator medical services. Somatic tumour gene panel testing has been demonstrated locally and internationally as best practice for the allocation of appropriate treatment, indicating disease prognosis and monitoring therapeutic outcomes.

There is increasing clinical and patient demand for multigene testing with patients experiencing large out of pocket costs raising issues of equity of access.

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:

The proposed test involves equivalent safety issues to current tissue pathology and haematology investigations.

The proposed service offers superior safety in comparison to non-identification of relevant genomic alterations where patients may receive ineffective treatment, experience delays in treatment or no treatment when treatment is possible.

The proposed service offers superior safety when testing is maximised on limited tissue samples and repeat biopsies of patients are avoided.

Clinical Effectiveness Outcomes:

The proposed service offers superior clinical effectiveness with the availability of more accurate, reliable and clinically valid tests.

The proposed service offers superior clinical effectiveness by providing the most appropriate treatment to the most applicable patients through tests proven to improve clinical decisions, integrated with the most current data relevant to the practice of medicine, and recognised as medically necessary to tailor treatment for the unique biology of a disease.

The proposed service offers superior clinical effectiveness because somatic gene panels can provide improved treatment outcomes compared to current publicly funded pathology tests.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

The proposed population are patients diagnosed with melanoma of the skin, lung cancer and colorectal cancer (CRC). Although large numbers of new cases of these cancers are diagnosed each year, only a minority of patients with advanced diseased require testing for genomic alterations to determine eligibility for specific targeted therapies.

The subset of cancer patients to be included in the proposed population can be determined from services undertaken in current MBS items: 73336 (unresectable stage III or stage IV metastatic cutaneous melanoma), 73337 (lung cancer with non-squamous or not otherwise specified histology (NSCLC)), 73341 (advanced or metastatic NSCLC) and 73338 (metastatic stage IV CRC) [1].

Medicare statistics indicate that a total of 8,444 services were undertaken for these item numbers from July 2015 to June 2016.

Therefore the proposed population is 8,500.

MBS Item	Services 2015
73336	1966
73337	3443
73338	2844
73341	191
Total	8444

1. Medicare Statistics

It is likely that the proposed population for this medical service will constitute approx. 20% of new cases of these cancers (15% of cutaneous melanomas, 31% of lung cancer and 16% of bowel cancer cases).

Cancer	Est. total new cases 2016 [2]	Applicable MBS items	MBS item services 2016	Est. % new cases tested
Melanoma	13282	73336	2025	15%
Lung	12203	73337 & 73341	3743	31%
Bowel	17250	73338	2844	16%
	42735		**8612**	**20%**

2. AIHW estimates new cases of bowel, lung and melanoma: Bowel cancer statistics, Lung cancer statistics, Melanoma of the skin statistics

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

Once at the time of diagnosis to determine treatment. Occasional follow up testing may be required to identify resistance to therapy.
Once per year is a reasonable average estimate.

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

Five

Note: patients with these cancers are unlikely to require follow up investigations beyond five years. Therefore, five years is a reasonable maximum estimate.

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

8,500

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

Uptake of the proposed medical service is estimated to increase on average at 3% per year (AIHW) indicating that the likely population in three years' time would be approx. 9,300 patients.

Leakage to populations not targeted by the service will be constrained by the MBS item number descriptors to ensure testing is applied only where clinically indicated. It is important to recognise that knowledge in this field is advancing rapidly with new diagnostic genetic aberrations increasingly reported. It is difficult to predict numbers of additional patients who may benefit from future advances in knowledge of actionable molecular aberrations in cancers with applicable targeted therapies. It may be beneficial to amend the new item number to include new testing and therapies as they become available in the future.

AIHW estimates new cases of bowel, lung and melanoma: Bowel cancer statistics, Lung cancer statistics, Melanoma of the skin statistics

PART 8 – COST INFORMATION

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

Equipment and resources	Per case
Multiple genes (ISH, PCR, small NGS panel): Cost of NGS for a minimum of 3 genes: • DNA and RNA extraction and quantification: $30 per sample • Kit: $250 per sample • Sequencing: $150 per sample • Labour (medical and scientific) and bioinformatics for interpretation: $170	$600
Total	**$600**

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

7 -10 working 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 (proposed category number) – (proposed category description)
Proposed item descriptor A panel test for the characterisation of gene rearrangements or somatic tumour mutations in a minimum of three genes, in neoplastic cells from patients with laboratory evidence of advanced cancer (including a service in items 73336, 73337, 73338 or 73341, if performed). The rearrangements or mutations must be clinically important and relevant to the patient's cancer type and requested by, or on behalf of, a specialist or consultant physician (Pathologist determinable). At least one of the targeted genes must be used to determine whether requirements for a targeted therapy listed on the Pharmacy Benefits Schedule (PBS) are fulfilled. Multigene panel (minimum 3 genes) Fee: $600

PART 9 – FEEDBACK

The Department is interested in your feedback.

54. How long did it take to complete the Application Form?

Insert approximate duration here

55. (a) Was the Application Form clear and easy to complete?

☐ Yes
☐ No

(b) If no, provide areas of concern:

Describe areas of concern here

56. (a) Are the associated Guidelines to the Application Form useful?

☐ Yes
☐ No

(b) If no, what areas did you find not to be useful?

Insert feedback here

57. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

☐ Yes
☐ No

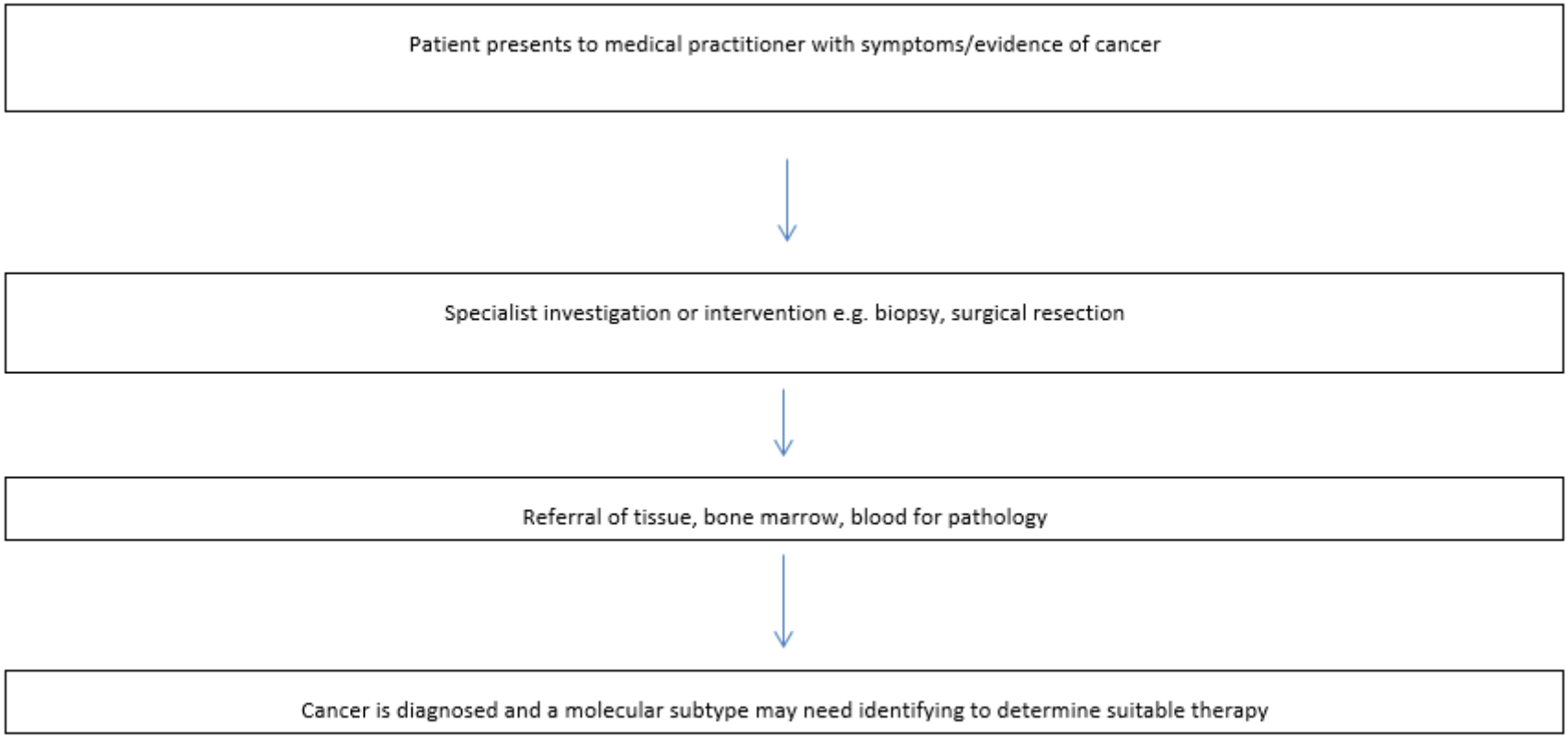
(b) If yes, please advise:

The form could be better tailored for Pathology items that are not technology-specific (i.e. not a single TGA product) and already have established rules in the MBS (Approved Pathology Practitioners; accredited laboratories; referrals by registered medical practitioners).

Appendix A Flowcharts

Q26 Current clinical pathway before intervention

Somatic tumour gene panel



Q40 Current clinical pathway after comparator

Somatic tumour gene panel