Australian Government

Department of Health

Application Form

BRAF V600 mutation testing to determine eligibility for PBS access to Braftovi® (encorafenib) in patients with metastatic colorectal cancer (stage IV)

(New and Amended Requests for Public Funding)

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): N/A
Corporation name: Pierre-Fabre Australia Pty Ltd
ABN: 30 098 999 850
Business trading name: Pierre-Fabre Australia Pty Ltd

Primary contact name: REDACTED

Primary contact numbers:
Business: REDACTED
Mobile: REDACTED
Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers:
Business: REDACTED
Mobile: REDACTED
Email: REDACTED

2. (a) Are you a lobbyist acting on behalf of an Applicant?

No.

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

Not applicable.

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

BRAF V600 mutation testing to determine eligibility for PBS access to Braftovi® (encorafenib) in patients with metastatic colorectal cancer (mCRC) (stage IV).

This is part of a co-dependent submission to the PBAC.

Detailed description:

This application proposes that BRAF V600 mutation testing is added to the MBS item (73338) which currently covers a test of tumour tissue from a patient with mCRC (stage IV), requested by a specialist or consultant physician, to determine if the requirements relating to rat sarcoma oncogene (RAS) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

This application contends that RAS mutation testing is determined using a somatic tumour gene panel test, which already routinely includes a BRAF V600 mutation test. Since the determination of BRAF mutation status will guide the use of encorafenib in the treatment of mCRC, this application seeks to formalise current clinical practice.

An application will be lodged with the PBAC to seek PBS listing of these medicines for the treatment of BRAF V600 mutated mCRC.

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)

Colorectal cancer is caused by an accumulation of mutations driving the transformation of cells lining the colon or rectum to polyps, which upon further mutations and growth can turn into cancerous adenocarcinoma cells. Approximately 50% of CRC cases are diagnosed at Stage III or IV when cancer has already spread to the lymph nodes or beyond.

Colorectal cancer is the second most common cancer in both men and women in Australia; is more common in people over the age of 50, and has a five-year survival rate of 69%. However, the five-year survival rate significantly decreases to 11% in metastatic disease.

Approximately 55% of mCRC patients are RAS wild type and 45% have the RAS mutation. BRAF mutations are estimated to occur in around 10% of patients with mCRC; RAS and RAF mutations are nearly always mutually exclusive. The V600 mutation is the most common BRAF mutation and the risk of mortality in patients with BRAF V600 mutation is higher than those with wild-type BRAF.

The BRAF V600 mutation identifies a distinct subtype of mCRC that has a poor prognosis with no targeted therapies currently available.

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 intention is to have specific mention of BRAF V600 mutation testing in the current MBS code for gene testing for mCRC, being MBS item 73338.

Currently, patients with the RAS gene mutation in mCRC have access to gene mutation testing under MBS item 73338 in order to receive targeted treatment with PBS funded cetuximab or panitumumab.

BRAF testing is not explicitly mentioned in MBS code 73338, but it is currently routinely performed and reported as part of next generation sequencing tumour gene panels. For example, the most widely used next generation panel is Find-It™, which is a 'focused' panel for colorectal testing, and which reports on the mutation status of 4 genes: RAS, BRAF, NRAS and PIK3CA.

Grouping the mutation testing for RAS and BRAF for patients with mCRC under the same MBS item number is logical, since this provides a more complete picture of gene mutation to best direct the choice

of subsequent therapeutic intervention. Both RAS and BRAF mutation status are determined using a gene panel test of the same tumour tissue sample.

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

☒ Yes
☐ No

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

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

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

Item number 73338.

(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):

As stated above, current gene testing for mCRC routinely tests for BRAF V600 mutation status, but this is not currently explicit in the MBS item descriptor. This application requests the amendment to the item descriptor to add BRAF testing in order fulfil eligibility requirements for access to PBS-funded encorafenib.

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

Not applicable.

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

☒ Yes
☐ No

(g) If yes, please advise:

This is a co-dependent technology application.

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

7. 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

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

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

9. (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

This application forms part of a co-dependent technology submission. Encorafenib is intended for use in metastatic (stage IV) colorectal cancer patients (mCRC) where a somatic tumour gene panel test will assist with determining suitability for therapy.

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

Encorafenib (with binimetinib) gained a recommendation for PBS listing for BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma at the November 2018 PBAC meeting

The treatment is not yet PBS listed for melanoma or mCRC.

(b) 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

REDACTED

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

Braftovi® (encorafenib)

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

Not applicable.

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

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)?

Not applicable.

☐ 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?

Not applicable.

☐ Yes
☐ No

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

11. 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.

A number of different assays that all require the use of consumables can be used to detect the genetic changes described above including fluorescent in situ hybridisation (FISH), polymerase chain reaction (PCR), Sanger sequencing, and next generation sequencing (NGS).

This application is not specific to 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

12. (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 to the test

(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

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

The test for gene mutation status is already available and in use in Australia.

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

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

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

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

Bio-Rad Laboratories Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 316116
Product name: Acquired genetic alteration IVDs
Sponsor: Bio-Rad Laboratories Pty Ltd
Manufacturer: Bio-Rad Laboratories Inc

Sysmex Australia Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 315997
Product name: Acquired genetic alteration IVDs
Sponsor: Sysmex Australia Pty Ltd
Manufacturer: Sysmex INOSTICS GmbH

AusDiagnostics Pty Ltd - Inborn/inherited genetic disorder IVDs
ARTG ID: 312306

Myriad Genetics Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 285557
Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Myriad Genetics Pty Ltd
Manufacturer: Myriad International GmbH

Elitechgroup Australia PTY LTD - Acquired genetic alteration IVDs
ARTG ID: 278596

Product name: Acquired genetic alteration IVDs
Sponsor: Elitechgroup Australia Pty Ltd
Manufacturer: ELITechGroup SpA

Key Diagnostics Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 270292
Product name: Acquired genetic alteration IVDs
Sponsor: Key Diagnostics Pty Ltd
Manufacturer: ViennaLab Diagnostics GmbH

Carl Zeiss Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 266568
Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Carl Zeiss Pty Ltd
Manufacturer: MetaSystems Probes GmbH

Agilent Technologies Australia Pty Ltd - Acquired genetic alteration…
ARTG ID: 264573
Product name: Acquired genetic alteration IVDs
Sponsor: Agilent Technologies Australia Pty Ltd
Manufacturer: Dako Denmark AS

Abacus dx Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 262298
Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Abacus dx Pty Ltd
Manufacturer: Biocartis NV

Abacus dx Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 256572
Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Abacus dx Pty Ltd
Manufacturer: ZytoVision GmbH

Thermo Fisher Scientific Australia Pty Ltd - Acquired genetic…
ARTG ID: 256113
Product name: Acquired genetic alteration IVDs
Sponsor: Thermo Fisher Scientific Australia Pty Ltd
Manufacturer: Microgenics Corporation

Abacus dx Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 255352
Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Abacus dx Pty Ltd
Manufacturer: Invivoscribe Technologies

Qiagen Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 238792
Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Qiagen Pty Ltd
Manufacturer: Qiagen GmbH

Vela Diagnostics Australia Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 235394
Product name: Acquired genetic alteration IVDs
Sponsor: Vela Diagnostics Australia Pty Ltd
Manufacturer: Vela Operations Singapore Pte Ltd

Vela Diagnostics Australia Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 228024
Product name: Acquired genetic alteration IVDs
Sponsor: Vela Diagnostics Australia Pty Ltd
Manufacturer: Vela Operations Singapore Pte Ltd

Cepheid Holdings Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 226631
Product name: Acquired genetic alteration IVDs
Sponsor: Cepheid Holdings Pty Ltd
Manufacturer: Cepheid

Bio-Strategy Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 226487
Product name: Acquired genetic alteration IVDs
Sponsor: Bio-Strategy Pty Ltd
Manufacturer: Nanostring Technologies Inc

Qiagen Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 226453
Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Qiagen Pty Ltd
Manufacturer: Qiagen GmbH

Sysmex Australia Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 225995
Product name: Acquired genetic alteration IVDs
Sponsor: Sysmex Australia Pty Ltd
Manufacturer: Cytocell Ltd

Qiagen Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 214994
Product name: Acquired genetic alteration IVDs
Sponsor: Qiagen Pty Ltd
Manufacturer: Qiagen Manchester Ltd

Sysmex Australia Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 214482
Product name: Acquired genetic alteration IVDs
Sponsor: Sysmex Australia Pty Ltd
Manufacturer: Sysmex Corporation

Abbott Australasia Pty Ltd Molecular Division - Human…
ARTG ID: 197099
Product name: Human genetics-related IVDs
Sponsor: Abbott Australasia Pty Ltd Molecular Division
Manufacturer: Abbott Molecular Inc

Roche Diagnostics Australia Pty Limited - Acquired genetic alteration …
ARTG ID: 196363
Product name: Acquired genetic alteration IVDs
Sponsor: Roche Diagnostics Australia Pty Limited
Manufacturer: Roche Diagnostics GmbH

Abbott Australasia Pty Ltd Molecular Division - Acquired genetic…
ARTG ID: 196286

Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Abbott Australasia Pty Ltd Molecular Division
Manufacturer: Abbott Molecular Inc

Roche Diagnostics Australia Pty Limited - Acquired genetic alteration …
ARTG ID: 194319
Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Roche Diagnostics Australia Pty Limited
Manufacturer: Roche Diagnostics GmbH

Roche Diagnostics Australia Pty Limited - Acquired genetic alteration …
ARTG ID: 192395
Product name: Acquired genetic alteration IVDs
Sponsor: Roche Diagnostics Australia Pty Limited
Manufacturer: Roche Diagnostics GmbH

Roche Diagnostics Australia Pty Limited - Acquired genetic alteration …
ARTG ID: 192394
Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Roche Diagnostics Australia Pty Limited
Manufacturer: Roche Diagnostics GmbH

Leica Biosystems Melbourne Pty Ltd - Acquired genetic alteration IVDs
ARTG ID: 191254
Product name: Acquired genetic alteration IVDs
Sponsor: Leica Biosystems Melbourne Pty Ltd
Manufacturer: Leica Biosystems Newcastle Ltd

Roche Diagnostics Australia Pty Limited - Acquired genetic alteration …
ARTG ID: 180933
Product name: Acquired genetic alteration IVDs - Acquired genetic alteration IVDs
Sponsor: Roche Diagnostics Australia Pty Limited
Manufacturer: Roche Diagnostics GmbH

14. 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?

Not applicable.

☐ Yes (please provide details below)

☐ No

REDACTED

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

Not applicable.

☐ Yes (please provide details below)

☐ No

PART 4 – SUMMARY OF EVIDENCE

16. **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.	Multicentre, open label, phase 3 randomised trial	Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer. Published as Kopetz S, et. Al. NEJM, 2019; 381: 1632-1643 NCT02928224; EudraCT number 2015-005805-35 BEACON study	Active, not recruiting. 665 patients with BRAF V600E-mutated metastatic colorectal cancer who had had disease progression after one or two previous regimens; randomly assigned 1:1:1 to: Triplet therapy = encorafenib, binimetinib, and cetuximab. Doublet therapy = encorafenib and cetuximab Control = investigators' choice of either cetuximab and irinotecan or cetuximab and FOLFIRI. Primary end points: overall survival and objective response rate (triplet-therapy group compared with the control group).	https://www.nejm.org/doi/full/10.1056/NEJMoa1908075	October 2019
2.	Safety study	Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, encorafenib, and cetuximab triplet therapy for patients with BRAF V600E–mutant metastatic colorectal cancer: safety lead-in results from the phase III BEACON colorectal cancer study. J Clin Oncol 2019; 37: 1460-9.	Lead in safety analysis prior to the randomisation phase of the BEACON study.	https://ascopubs.org/doi/full/10.1200/JCO.18.02459?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed	2019 Companion paper to Ref 1. Above.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3.	Review	Sharma, SG, Gulley, ML. BRAF Mutation Testing in Colorectal Cancer Arch Pathol Lab Med. 2010;134:1225–1228	This review describes: • The role of BRAF in the pathogenesis of CRC; • Analytical methods to identify BRAFV600E mutation; • Use of BRAF and KRAS mutation analysis to select appropriate therapies for the treatment of CRC.	https://www.archivesofpathology.org/doi/10.1043/2009-0232-RS.1?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed	2010

** 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.*

17. 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.	Phase II, Open-label, Single Arm, Multicenter Study	Encorafenib, Binimetinib and Cetuximab in Subjects With Previously Untreated BRAF-mutant ColoRectal Cancer (ANCHOR-CRC). Recruiting. Estimated enrolment 90 participants. NCT03693170	The purpose of this study is to evaluate the efficacy and safety of the combination of study drugs encorafenib, binimetinib and cetuximab in patients who have BRAF V600E mutant metastatic colorectal cancer and have not received any prior treatment for their metastatic disease.	www.clinicaltrials.gov	Estimated primary completion date: June 2020
2.	Phase I/II, open-label, single arm, study	Phase I/II Trial of Encorafenib, Binimetinib, and Nivolumab in Microsatellite Stable BRAFV600E Metastatic Colorectal Cancer. Active, not yet recruiting. Estimated enrolment: 38 participants. NCT04044430	This phase I/II trial studies the side effects and how well encorafenib, binimetinib, and nivolumab work in treating patients with metastatic, microsatellite stable, BRAFV600E gene-mutated colorectal cancer.	www.clinicaltrials.gov	Estimated primary completion date: June 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

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

    The Royal College of Pathologists of Australasia (RCPA), Public Pathology Australia, Australian Pathology.

    REDACTED

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

    Clinical Oncology Society of Australia (COSA), Medical Oncology Group of Australia (MOGA).

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

    Bowel Cancer Australia, Cancer Voices Australia, Cancer Council Australia.

    REDACTED

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

    N/A

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

    REDACTED

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

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

23. 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 application relates to a test to determine the appropriate use of encorafenib in patients with mCRC.

REDACTED

Colorectal cancer (CRC) or bowel cancer is a cancer of the colon or rectum, caused by an accumulation of mutations driving the transformation of cells lining the colon or rectum to polyps, which upon further mutations and growth can turn into cancerous adenocarcinoma cells.[1] CRC is the third most common cancer in men and the second in women. The highest incidence rates were in Northern America, Australia, New Zealand, Europe, and South Korea. Rates are lower in Africa and South-Central Asia.[2]

Colorectal cancer is a progressive, multistep genetic disease, influenced by a variety of genes and environmental factors. Colorectal carcinomas first develop from pre-existing adenocarcinoma cell polyps.[3] Eventually, sequential alterations to various tumour-suppressor genes and oncogenes result in the progression of adenocarcinoma cells to cancerous cells, thus polyps develop into tumours.[4] This process is known as the adenoma-carcinoma sequence. Furthermore, cancerous cells can alter their genetic and epigenetic profiles and thus acquire invasion capability, spreading to other organs (metastases) such as the liver and lung.[5]

Early stage CRC is usually asymptomatic or does not present with specific manifestations leading to delayed or (mis)diagnosis. Common misdiagnoses include haemorrhoids, polyps, ulcerative colitis and Crohn's disease. Differential diagnosis is needed via colonoscopy, biopsy and imaging.[6] The tumour staging of CRC is as follows:

TNM stage	Location	Definition
I	Local	Cancer is located in the innermost lining of the bowel
II	Local	Cancer has grown through the muscle layer of the bowel
III	Regional	Cancer has spread to at least one lymph node close to the bowel
IV	Metastatic	Cancer has spread in the body

Metastatic colorectal cancer (mCRC)

Development of metastasis is a concern for patients and clinicians alike as metastasis may be fatal, causing mass-effect and meddling with homeostasis7. Approximately 50% of CRC cases are diagnosed at Stage III or IV when cancer has already spread to the lymph nodes or beyond: 20% to 25% are initially diagnosed at metastatic stage; 10 to 25% at the time of the resection of the primary colorectal cancer. The incidence is

[1] Goel A, Boland CR. Recent insights into the pathogenesis of colorectal cancer. Current opinion in gastroenterology 2010; 26:47-52
[2] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. European journal of cancer 2013;49:1374-403
[3] Bardhan K, Liu K. Epigenetics and colorectal cancer pathogenesis. Cancers 2013; 5:676-713
[4] Dekker E, van Gulik T. Colorectal cancer: what the clinician wants to know. Cancer imaging: the official publication of the International Cancer Imaging Society 2005;5 Spec No A:S127-32
[5] Bardhan K, Liu K. Epigenetics and colorectal cancer pathogenesis. Cancers 2013;5:676-713
[6] https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/signs-and-symptoms.html, consulted Sept 2018; 2. https://www.cancercenter.com/colorectal-cancer/symptoms/, consulted Sept 2018
[7] Sci Rep. 2016; 6: 29765. Published online 2016 Jul 15. doi: 10.1038/srep29765. Patterns of metastasis in colon and rectal cancer. Matias Riihimäki, Akseli Hemminki,Jan Sundquist, and Kari Hemminki

higher (35%) when a computed tomography (CT) scan is used;8 and 50% of new non-metastatic CRC cases will evolve to a metastatic stage within one year9. The liver is second only to the lymph nodes as the most common part of the body for bowel cancer cells to spread to.

Burden of mCRC

Colorectal cancer is a major cause of morbidity and mortality throughout the world. It accounts for over 9% of all cancer incidences. It has become the world's fourth most common in terms of cancer mortality with 20-25% of patients diagnosed at the most extended cancer stage (IV).10 11 CRC is the second most common cancer in both men and women in Australia and is more common in people over the age of 50 and has a five-year survival rate of 69%. In 2016, there were 5,375 deaths caused by bowel cancer in Australia. This represents the second highest number of cancer deaths in Australia.12

A total of 11% of cancer costs are due to CRC - the 2nd most expensive cancer in the EU and the 1st in Australia in that CRC costs in excess of €10 billion in the EU and $283 million in Australia.13

In the last decades, a significant increase in the life expectancy of patients with CRC has been achieved with different diagnostic and treatment programs. Despite these improvements, the presence of metastasis, disease recurrence, and advanced local tumours continue to remain poor prognostic factors.

Statistics from the US show that the five-year survival rate of people with localised stage CRC is 90%. If the cancer has spread to surrounding tissues or organs and/or the regional lymph nodes, the five-year survival rate is 71%. If the cancer has spread to distant parts of the body and is therefore considered as metastatic cancer, the five-year survival rate significantly decreases to 13%. Approximately 20% of CRC patients present with synchronous distant metastases at the initial diagnosis, and about 50% of the patients without metastases at presentation develop distant metastases within three years of diagnosis.14

Median survival without treatment is less than 8 months from the moment of its presentation, and a survival rate at 5 years of 11% is the best prognosis for those who present with local metastasis. Even in patients with limited metastatic disease, 5-year survival is exceptional. Patients with hepatic metastasis of colorectal cancer have a median survival of 5 to 20 months with no treatment. Approximately 20 to 30% of patients with colorectal metastasis have disease confined to the liver, and this can be managed with surgery. Modern surgical strategies at the main hepatobiliary centres have proved that hepatectomy of 70% of the liver can be performed, with a mortality rate of less than 5%.

24. 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:

Specific patient characteristics

Approximately 55% of mCRC patients are RAS wild type and 45% have the RAS mutation. BRAF mutations are estimated to occur in around 10% of patients with mCRC; RAS and RAF mutations are nearly always mutually exclusive.

[8] Euroasian J Hepatogastroenterol. 2017 Jul-Dec; 7(2): 166–175. Published online 2017 Sep 29. doi: 10.5005/jp-journals-10018-1241. Hepatic Metastasis from Colorectal Cancer. Alan I Valderrama-Treviño, Baltazar Barrera-Mera, Jesús C Ceballos-Villalva, and Eduardo E Montalvo-Javé

[9] NCCN Guideline: Rectal cancer staging, 2015; 2. Cancer research UK: Bowel cancer incidence by stage at diagnosis, 2018; 3. HAS: Evaluation Vectibix, 2014; 4. HAS: Evaluation Avastin, 2016

[10] Adam R, de Gramont A, Figueras J, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer treatment reviews 2015;41:729-41

[11] Clin Colon Rectal Surg. 2009 Nov; 22(4): 191–197. doi: 10.1055/s-0029-1242458. Colorectal Cancer. Guest editor Robin P. Boushey M.D., Ph.D. Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors. Fatima A. Haggar, M.P.H.1,2 and Robin P. Boushey, M.D., Ph.D.1

[12] Cancer Council Australia https://www.cancer.org.au/about-cancer/types-of-cancer/bowel-cancer/

[13] Luengo-Fernandez R et al., 2013; 2. OHE: Improving Efficiency and Resource Allocation in future Cancer Care, 2016 3. Australian Institue of Health and Welfare: Health system expenditure on cancer and other neoplasms in Australia 2008-09, 2013

[14] Cancer.net. Colorectal Cancer Statistics. 2016. http://www.cancer.net/cancer-types/colorectal-cancer/statistics & National Cancer Institute. Surveillance, Epidemiology and End Results Program. SEER Stat Fact Sheets: Colon and Rectum Cancer. 2016. https://seer.cancer.gov/statfacts/html/colorect.html

The BRAF mutation identifies a distinct subtype of mCRC that has a poor prognosis with no targeted therapies currently available. BRAF positivity in CRC 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.15

The V600 mutation is the most common BRAF mutation and the risk of mortality in the patients with these patients is higher than those with wild-type BRAF16. Studies with irinotecan-based chemotherapy have poor outcomes and expected median OS with 2nd and 3rd-line irinotecan-based chemotherapy standard of care is 5.9 months, median PFS of 4 months, and ORR of 4%. BRAF inhibitors are not effective alone due to the feedback activation of EGFR in BRAF-mutant CRC, leading to continued cell proliferation, and hence the rationale for the combination of binimetinib + encorafenib and cetuximab.16

Investigation, referral and management

Patients may present to a General Practitioner and subsequently are referred to a specialist oncology centre or physician. The optimal treatment strategy for patients with mCRC is generally discussed in a multidisciplinary expert team.

Clinical or biochemical suspicion of metastatic disease is confirmed by adequate radiological imaging [usually a computed tomography (CT) scan or, alternatively, magnetic resonance imaging (MRI) or ultrasonography]. A PET scan can be useful in determining the malignant characteristics of tumoural lesions, especially when combined with a CT scan or in the case of elevated tumour markers without indications of the location of relapse on CT scan in the surveillance of CRC.

A PET scan is also especially useful to characterise the extent of metastatic disease and to look for extrahepatic metastases (or extrapulmonary metastases) when the metastases are potentially resectable.

Histology of the primary tumour or metastases is always necessary before chemotherapy is started. For metachronous metastases, histopathological or cytological confirmation of metastases should be obtained, if the clinical or radiological presentation is atypical or very late (e.g. later than 3 years) after the initial diagnosis of the primary tumour.

All patients with mCRC undergo a test of tumour tissue to determine their gene status and hence eligibility for PBS subsidised treatment with cetuximab or panitumumab. Currently, item 73338 provides for testing of RAS mutations to limit subsidy of anti-EGFR antibodies to only those patients demonstrated to have no RAS mutations:

Item 73338

A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist or consultant physician, to determine if the requirements relating to rat sarcoma oncogene (RAS) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if:

> *(a) the test is conducted for all clinically relevant mutations on KRAS exons 2, 3 and 4 and NRAS exons 2, 3, and 4; or*
>
> *(b) a RAS mutation is found.*

Importantly in Australia, most of the colorectal RAS testing is done with next generation sequencing panels, and BRAF is routinely reported along with RAS under item 73338.

REDACTED

Larger hospitals have their own pathology testing and some have their own next generation sequencing panels. REDACTED

[15] 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

[16] Sorbye et al. High BRAF Mutation Frequency and Marked Survival Differences in Subgroups According to KRAS/BRAF Mutation Status and Tumor Tissue Availability in a Prospective Population-Based Metastatic Colorectal Cancer Cohort, 2015

The use of somatic gene panels minimises the cost of testing for multiple tumour markers and decreases the risk of treatment with inappropriate therapies. BRAF positivity in CRC 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.

25. 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 mCRC investigation and treatment:

- Patient presents to specialist medical practitioner with evidence of cancer
- Patient is referred for biopsy for pathological investigation
- Diagnosis of mCRC is reported
- The treating specialist requests further pathological investigations on the biopsy material to identify genomic alterations to the RAS and BRAF genes to determine appropriate PBS subsidised therapy

PART 6b – INFORMATION ABOUT THE INTERVENTION

The test is intended for patients with mCRC to determine eligibility for BRAF targeted treatment with encorafenib.

Currently, all patients in Australia with mCRC undergo a test of tumour tissue to ascertain the gene mutation status of the tumour. This is used to determine both prognostics for the patient and their targeted treatment. The MBS code 73338 allows for testing to determine RAS mutation status of a patient to determent their eligibility for panitumumab or cetuximab.

In Australia, most of the colorectal RAS testing is done with next generation sequencing panels, and BRAF is reported routinely along with RAS in these panels.

These tests are well established in Australia, with a number of validated and TGA approved methodologies. Validation of the test used in the key encorafenib clinical trial (BEACON) vs the test(s) commonly used in Australia will be presented in the submission, if necessary.

This application therefore does not request any change to either the number of tests performed or additional tests on the tissue samples, but rather that the current routine testing which includes BRAF be explicitly identified in the MBS item descriptor for item 73338.

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

This is the same procedure using the same sample test as currently occurs for MBS item 73338, i.e., a test of tumour tissue from a patient diagnosed with mCRC to identify genomic alterations in cancer cells. Testing methods include In situ hybridization (ISH), polymerase chain reaction (PCR) and next generation sequencing (NGS) methodologies among others.

As previously outlined, diagnosis and tumour staging are made from biopsy samples which are expected to provide sufficient tumour material to also carry out BRAF V600 testing, consistent with current practice for RAS testing in patients with mCRC.

BRAF V600 testing would ordinarily be ordered by the patient's surgeon or oncologist once a diagnosis of mCRC is made. A surgeon or oncologist is typically responsible for the collection of a biopsy or cytological sample from the patient. Tissue samples are normally processed into FFPE tissue blocks which are then sectioned, stained and mounted onto glass slides. Following mounting, samples are subsequently examined by a suitably qualified pathologist.

Once the tissue sample has been retrieved by the testing laboratory, an anatomical pathologist would mark the tumour; and a scientist would subsequently perform a dissection of the tumour cells (sample enrichment) so that an appropriate sample is available for DNA extraction and an assay would be

performed by a molecular scientist or technician, under the supervision of a senior scientist or pathologist in accordance with NPAAC laboratory supervision standards.

All BRAF mutation tests must occur in NATA accredited laboratories. Competence to perform the test is already being monitored through an RCPA quality assurance program (QAP). As the test is already being performed in the metastatic melanoma setting, no further investment in equipment is expected. Since BRAF testing is already being performed in the colorectal gene testing panels, no significant change in the number of tests being performed is expected as outlined later in this application.

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

No.

28. 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.

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

It is anticipated that most patients would require only one test per lifetime. Re-testing may be required in a small minority of patients if insufficient DNA is retrievable from biopsy cells, if the biopsy sample is not considered satisfactory (due to deterioration or formalin associated artefacts) or if DNA testing is inconclusive.

30. 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:

Not applicable.

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

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

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

Not applicable.

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

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

34. 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 continue to be delivered only by Approved Pathology Practitioners in Accredited Pathology Laboratories (as defined in MBS Pathology table).

35. (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:

Not applicable.

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

☒ Yes
☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

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

Testing for BRAF mutation status in mCRC is proposed as an amendment to the current MBS item descriptor for item 73338, to align with current clinical practice. The 'comparator' is therefore MBS item 73338, with its current item descriptor.

As shown in Part 2 above, the current MBS code 73338 allows for testing to determine RAS mutation status of a patient to determent their eligibility for panitumumab or cetuximab. Currently, most of the colorectal RAS testing is done with next generation sequencing panels, and BRAF is reported routinely along with RAS in these panels.

This application therefore does not request any change to either the number of tests performed or any additional tests on the tissue samples. Rather, the application proposes that the current routine testing, which includes BRAF, be explicitly stated in the item descriptor for MBS item 73338 to fulfil the requirements relating to BRAF V600 gene mutation status for access to encorafenib under the PBS.

38. 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

The application is to specify BRAF V600 testing in the existing item descriptor for MBS item 73338.

39. 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):

Currently, the panel test reports on a number of mutations, but the MBS explicitly funds testing to determine RAS mutation status in order for the patient to be eligible for cetuximab or panitumumab.

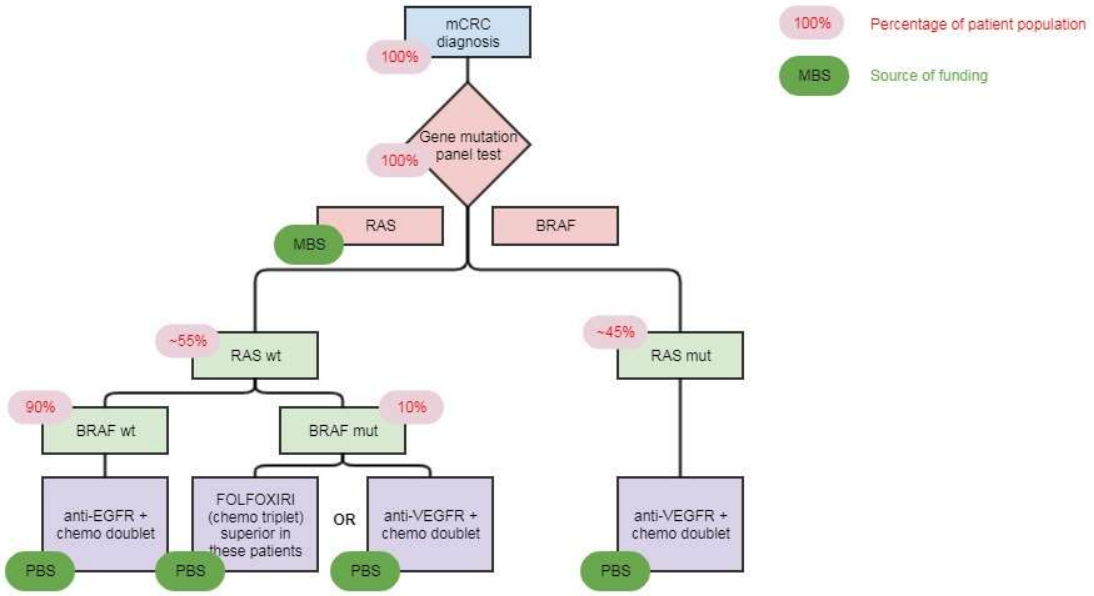
The tumour gene panel tests run under MBS code 73338 also provide information on BRAF mutation status which is used by clinicians for prognostic indicators, but there are currently no treatments on the PBS specifically for patients with the BRAF mutation.

BRAF testing is currently not funded for patients with mCRC, but is funded under MBS item 73336 to determine eligibility for PBS funded dabrafenib or vemurafenib to treat metastatic melanoma (refer to successful minor application to add treatment with encorafenib and binimetinib in the descriptor for MBS item 73336). REDACTED

BRAF positive CRC 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. Inclusion of BRAF reporting in the existing panel tests would allow for targeted treatment with encorafenib.

The current clinical algorithm is as follows:

Figure 1 Current gene mutation testing and treatment pathway for patients diagnosed with mCRC



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

☒ Yes
☐ No

Noting that BRAF testing is performed routinely in the colorectal gene panel tests which are used to determine RAS mutation status under MBS item 73338. Therefore, no significant change to the current testing practices is expected in response to this application.

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

Not applicable.

41. 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 delivery pathways for the MBS will not change, REDACTED, ostensibly for RAS mutation status but also, as shown in the sections above, these tests already report on a raft of genetic results, including BRAF.

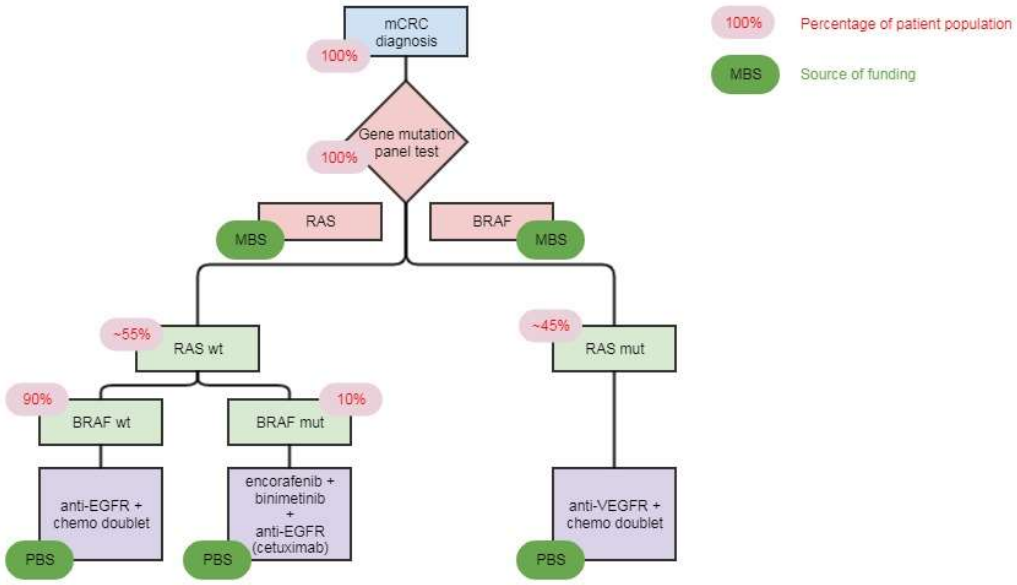
The clinical benefit of establishing BRAF mutation status for patients with mCRC derives from the change in pharmaceutical management of patients, once the co-dependent technology is funded by the PBS.

Currently, standard treatment for patients determined not to harbour the RAS gene mutation (RAS wild type) is an anti-EGFR + chemotherapy doublet. In patients who are determined to harbour the BRAF

mutation (through the current colorectal gene panel testing), an anti-VEGFR + chemotherapy doublet OR chemotherapy triplet (e.g. FOLFOXIRI) would be trialled, however these treatments are associated with modest clinical benefit in patients harbouring the BRAF V600 mutation.

Compared to standard of care, the Phase 3 BEACON clinical trial demonstrates a significant clinical benefit of triplet therapy (encorafenib + binimetinib and cetuximab) in patients with BRAF V600 mutated disease.

Figure 2 Proposed gene mutation testing and treatment pathway for mCRC patients following MSAC approval of BRAF testing and PBAC approval of treatment with encorafenib (+binimetinib and cetuximab)



PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

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

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

Please advise if the overall clinical claim is for:

☒ Superiority
☐ Non-inferiority

43. 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:
Toxic effects from subsequent treatment
Adverse events associated with biopsy
Rate of re-biopsy
Impact on patients of false positive and false negative test results

Clinical Effectiveness Outcomes:

Overall survival (OS)

Objective response rate (ORR)

Progression free survival (PFS)

Analytic validity

It is anticipated that data will be presented to demonstrate the analytic accuracy of Australian tests in colorectal specimens and a comparison of the test methodology between Australian laboratories and the test methodology used in the Phase 3 pivotal clinical trial (BEACON).

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

The proposed population are patients with mCRC (Stage IV). In 2015, there were 15,604 new cases of CRC diagnosed in Australia (AIHW 2018, AIHW 2019). In 2019, it is estimated that 16,398 new cases of colorectal cancer will be diagnosed in Australia.

Although large numbers of new cases of CRC are diagnosed each year, a smaller proportion of patients will have mCRC that is not resectable, and so a smaller number will undergo testing for genomic alterations to determine eligibility for specific targeted therapies. An Australian population study of the NSW Cancer Registry of patients diagnosed during 2000-2007 were followed to December 2011 for subsequent metastases: 26.4% of the cases initially diagnosed with localised or regional colon cancer had developed metastatic disease, as had 29.5% of the rectal cancer cases.[17] Another study states that 20% (to possibly 50%) of patients with stage II or III disease will progress to stage IV at some point during the course of their disease.[18] Therefore, a rough average of 20 - 26% of CRC will develop into metastatic disease, or approximately 3,200 to 4,160 cases.

The subset of cancer patients to be included in the proposed population can be determined from services currently undertaken for MBS item 73338 as BRAF testing is routinely performed with RAS testing (under item 73338), utilising next generation sequence panels.

Year	Total Services
2013/2014	52
2014/2015	1,462
2015/2016	2,844
2016/2017	2,397
2017/2018	2,187
2018/2019	2,434
Total	11,376
Mean (Jul 2015-Jun 2019)	2466

In July 2018, MSAC considered the considered real world data (RWD) on utilisation of item 73338, following Applications 1362 and 1363: RAS mutation testing for eligibility for cetuximab and panitumumab in previously untreated mCRC patients. MSAC recalled that it was predicted that item 73338 would be utilised by 2208 patients in the first year, increasing to 2465 patients by year 5.

Updated Medicare statistics indicate that an average of 2,466 services were undertaken for item 73338 from July 2015 to June 2019. This is closely aligned with the numbers presented in Applications 1362 and 1363 and later validated by real world data.

As there is no clinical rationale for testing for BRAF in the absence of the RAS test, then explicitly including the BRAF test in item 73338 is not likely to increase the number of services delivered; establishing RAS status is a priority in terms of not using EGFRs in RAS mutation patients.

It therefore follows that the frequency of services for RAS testing informs the number of BRAF tests that will be done (i.e. no change to current rate of testing).

[17] Cancer Epidemiol. 2017 Aug;49:92-100. doi: 10.1016/j.canep.2017.05.012. Epub 2017 Jun 6. Colorectal cancer metastatic disease progression in Australia: A population-based analysis. Luo Q, O'Connell DL, Kahn C, Yu XQ.

[18] Predictors of Survival in Stage IV Metastatic Colorectal Cancer. MICHALIS ZACHARAKIS et al. Anticancer Research February 2010 vol. 30 no. 2 653-660.

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

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

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

Not applicable.

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

It is estimated that approximately 2,466 patients will utilise the medical service in Year 1. This number will be refined and validated in the submission.

48. 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 remain relatively constant, as evident by the historical utilisation data presented in question 46.

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

PART 8 – COST INFORMATION

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

The current fee for item 73338 is as follows:

Fee: $362.60 **Benefit:** 75% = $271.95 85% = $308.25

REDACTED

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

It is anticipated that the service will take approximately 7-10 working days.

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

Proposed additions to the descriptor for item 43338 are italicised below.

Category 6 – PATHOLOGY SERVICES
73338 Proposed item descriptor: A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist or consultant physician, to determine if: 1. the requirements relating to rat sarcoma oncogene (RAS) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if: (a) the test is conducted for all clinically relevant mutations on KRAS exons 2, 3 and 4 and NRAS exons 2, 3, and 4; or (b) a RAS mutation is found ***2. the requirements relating to BRAF V600 gene mutation status for access to encorafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled***