



Australian Government

Department of Health

Application Form

(New and Amended Requests for Public Funding)

(Version 2.5)

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.

The application form will be disseminated to professional bodies / organisations and consumer organisations that have will be identified in Part 5, and any additional groups that the Department deem should be consulted with. The application form, with relevant material can be redacted if requested by the Applicant.

Should you require any further assistance, departmental staff are available through the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: Merck Sharp & Dohme (Australia) Pty Limited

ABN: redacted

Business trading name: redacted

Primary contact name:

Primary contact numbers

Business: redacted

Mobile: redacted

Email: redacted

Alternative contact name:

Alternative contact numbers

Business: redacted

Mobile: redacted

Email: redacted

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

Yes

No

(b) If yes, what is the Applicant(s) name that you are acting on behalf of?

Insert relevant Applicant(s) name here.

3. (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

4. Application title

Pembrolizumab (MK-3475) in Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma

5. 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)

Stage IV Colorectal Carcinoma (CRC) who are receiving first line (1L) treatment

6. 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)

ImmunoHistoChemistry (IHC) test for identification of Mismatch Repair Deficiency (dMMR) for access to pembrolizumab in patients with Stage IV CRC

7. (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:

As IHC testing for MMR is already routinely performed in most pathology centres under item 72847 (4-6 antibodies), this item could be augmented for testing for eligibility for pembrolizumab.

(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:

PBS funding will be sought for pembrolizumab treatment of those CRC patients who are found to be dMMR.

8. 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

9. 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
- vi. Is for genetic testing for heritable mutations in clinically affected individuals and, when also appropriate, in family members of those individuals who test positive for one or more relevant mutations (and thus for which the Clinical Utility Card proforma might apply)

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

- Pharmaceutical / Biological
- Prosthesis or device
- No

11. (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):

Insert PBS item code(s) here

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

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

We intend to submit the PBAC application in March 2017

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

Trade name: KEYTRUDA

Generic name: Pembrolizumab

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

Yes

No

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 Protheses 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

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

Single use consumables: Not applicable

Multi-use consumables: Not applicable

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (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: Class II In-vitro diagnostic test (GMDN CT1056)

Manufacturer's name: Various (see listing in next row)

Sponsor's name: Various (In house, Dako, Biospecifix, Roche, Thermo Fisher, MetaGene, Abacus ALS, Becton Dickinson, Beckman Coulter, Life Technologies, Leica, Diagnostic Solutions,

- (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

15. (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: 279628, 269420, 240833, 239099, 216549, 248292, 224218, 175635, 262536, 183436, 229929, 240833, 224829, 224373, 214553, 212747, 208140, 178442

TGA approved indication(s), if applicable: Insert approved indication(s) here

TGA approved purpose(s), if applicable: To be used in histology and cytology to provide information about the presence and localisation of specific proteins and antigens present in histological tissue sections, cytological smears and fluids

(Please note that all of the above registered tests have approval to be used for IHC testing of tissue section proteins. As MSD is not pairing with a specific test manufacturer, we have left the response to this question broad to accommodate different laboratory practices. However, this does not necessarily mean that all of these tests will be used in practice.)

16. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

Yes (please provide details below)

No

Date of submission to TGA: Insert date of submission here

Estimated date by which TGA approval can be expected: Insert estimated date here

TGA Application ID: Insert TGA Application ID here

TGA approved indication(s), if applicable: If applicable, insert description of TGA approved indication(s) here

TGA approved purpose(s), if applicable: If applicable, insert description of TGA approved purpose(s) here

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

Yes (please provide details below)

No

Estimated date of submission to TGA: Insert date of submission here

Proposed indication(s), if applicable: If applicable, insert description of proposed indication(s)

Proposed purpose(s), if applicable: If applicable, insert description of proposed purpose(s) here

PART 4 – SUMMARY OF EVIDENCE

18. 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.	Single-arm (Phase II)	Le DT et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency (KEYNOTE-16). NEJM; 372(26):2509-20. NCT01876511	Design: Phase 2 study in patients with metastatic carcinoma +/- MMR deficiency. Intervention: Pembrolizumab Population: MMR-deficient CRC=11 patients, MMR-proficient CRC=21 patients and non-CRC = 9 patients. Results: Objective response and progression-free survival rates were 40% and 78%, respectively, for MMR-deficient CRC and 0% and 11% for MMR-proficient CRC.	link to article	25 Jun 2015
2.	Clinical guidelines	Royal College of Pathologists of Australasia. CRC Structured Reporting Protocol.	These guidelines provide indicators of the minimum requirements of the Royal College of Pathologists of Australasia for testing in Colorectal Cancer. Section G4.01 provide recommendations in relation to the procedures for testing mismatch repair deficiency status.	link to article	May 2016
3.	Diagnostic accuracy	Ward R et al. Routine testing for mismatch repair deficiency in sporadic colorectal cancer is justified. J Pathol. 2005 ;207(4):377-84.	Design: Prospective cohort study on a consecutive series of fresh tissue samples at one Australian institution Aim: To examine the accuracy of IHC staining (MLH1 and MSH2 only) in the identification of MMRd CRC in routine clinical practice. Results: Sensitivity was 83% and Specificity was 98%.	link to article	Dec 2005

	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 ***
4.	Diagnostic Accuracy	Lindor NM et al. Immunohistochemistry Versus Microsatellite Instability Testing in Phenotyping Colorectal Tumors. J Clin Oncol 2002; 20: 1043-8.	Design: Colorectal cancers from 1,144 patients at 3 centres were assessed. Aim: To compare microsatellite instability (MSI) testing with immunohistochemical (IHC) detection of hMLH1 and hMSH2 in colorectal cancer. Results: Sensitivity was 92.3% and specificity was 100% for DNA mismatch repair defects.	link to article	Feb 2002
5.	Literature review of Diagnostic Accuracy Studies	Shia J. Immunohistochemistry versus Microsatellite Instability Testing For Screening Colorectal Cancer Patients at Risk For Hereditary Nonpolyposis Colorectal Cancer Syndrome. J Mol Diagn 2008, 10:293–300.	Design: A review of the literature, including studies that conducted IHC on MLH1, MSH2, PMS2 and MSH6 proteins. Aim: To identify studies that report on the utility of IHC testing for dMMR. Results: Including PMS2 and MSH6 proteins in IHC MMR testing has improved its sensitivity to 94%.	link to article	July 2008
6.	Pathologist Survey	Mascarenhas L et al. A survey of the current provision of screening tumours for mismatch repair deficiency in Australia: An Inherited Cancer Connect Partnership initiative. COSA 42nd Annual Scientific Meeting 2015 Nov, Hobart, Australia	Design: Heads of RCPA accredited laboratories in Australia were surveyed. Aim: To survey the current availability of screening for CRC tumour MMRd. Results: The response rate was 76%. 94% of laboratories conducted MMR IHC testing. 54% are routinely screening all specimens for MMR.	link to article	Nov 2015

* 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.

19. 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.	RCT (Phase III)	KEYNOTE-177 (NCT02563002)	Design: Phase III, multi-center, international, randomized, open label, controlled trial of in subjects who have stage IV MSI-H or dMMR CRC Intervention: Pembrolizumab (MK-3475) monotherapy versus standard chemotherapy. MSI testing will be undertaken by IHC or PCR Population: Estimated enrolment of 270 CRC MSI-H or dMMR patients	link to article	End of 2018
2.	Single-arm (Phase II)	KEYNOTE-164 (NCT02460198)	Design: Multi-center, open label, two-stage, phase 2 study of three cohorts (MSI positive CRC, MSI negative CRC, MSI positive solid non-CRCs) Intervention: Pembrolizumab 10mg/kg every 2 weeks Population: Estimated enrolment of 25 CRC (MSI positive and negative) patients is planned.	link to article	End of 2017
3.	Non-comparative trial (Phase II)	A Study of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Colon Cancer (CheckMate 142) (NCT02060188)	Design: International Phase 2, open-label, non-comparative trial in recurrent or metastatic CRC, including patients with and without MSI-H. The MSI-H part of the trial is non-randomized. Intervention: Nivolumab as a single-agent or in combination with Ipilimumab. Population: Estimated enrolment of 96 CRC patients (MSI-H and MSS).	link to article	Sep 2016
4.	Single-arm (Phase II)	Evaluate the Efficacy of MEDI4736 in Immunological Subsets of Advanced Colorectal Cancer (NCT02227667)	Design: Single arm, phase II study of CRC patients with MSI-H cancers. Intervention: MEDI4736 via IV infusion. Subjects will continue treatment for 12 months, or until progression of disease, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment occur. Population: Estimated enrolment of 48 CRC patients with MSI-H status	Link to article	July 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.

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

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 20. 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):**

Royal College of Pathologists

(IHC testing of MMR is already undertaken under MBS item #72847, so we have not requested a letter of support to comment on the service or the fee. Please refer to “COLORECTAL CANCER STRUCTURED REPORTING PROTOCOL” for the College’s specific recommendations on dMMR IHC testing [items CG4.01-CG4.02])

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

Medical Oncology Group of Australia

- 22. 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

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

MSD is not aligning with any specific manufacturer for this application. Therefore, the current manufacturers would be used for the IHC MMR test.

- 24. 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

25. 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:

Colorectal cancer (CRC) is cancer in any part of the large bowel (colon or rectum). If untreated, CRC can grow into the deeper layers of the bowel wall. It can spread from there to the lymph nodes (glands) and eventually metastasise. Stage IV CRC is defined as cancer that has spread to distant organs or tissues.

CRC is the second most common cause of cancer-related death after lung cancer for males and breast cancer for females in Australia (AIHW, 2010). Australia and New Zealand have one of the highest incidences of CRC worldwide with age-standardized rates of 44.8 and 32.2 per 100,000 in men and women, respectively (Ferlay, 2015). Mortality rates are lower at 5.2 and 3.6 deaths per 100,000 population in men and women, respectively. The lifetime risk of CRC to age 75 years in Australia is 1 in 18 (5.5%) for men and 1 in 26 (3.9%) for women (AIHW, 2010). In 2012, 14,957 new cases of bowel cancer were diagnosed in Australia (Bowel Cancer Australia).

CRCs may be divided via molecular phenotypes into tumours with normal DNA mismatch repair (MMR) function and those with DNA MMR deficiency (dMMR). The prevalence of dMMR is 14-16% in early metastatic CRC and 4% in Stage IV CRC and has a high mutation burden.

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

The proposed patient population includes patients diagnosed with Stage IV CRC receiving their first line of therapy. The median age of this patient population is expected to be approximately 70 years but could range from 20 to 100+. The male to female ratio is roughly 1:1. Due to the age of the cohort, various age-related comorbidities are likely to be present.

Patients who present with symptoms of CRC will receive further investigations. If these are suggestive of cancer, patients are referred for colonoscopy. Other patients may be identified through screening colonoscopies. To identify metastases, computerised tomography (CT) scans, magnetic resonance imaging (MRI) scans, positron emission tomography (PET) scans, abdominal ultrasound, endorectal ultrasound and chest X-rays may also be undertaken. Once diagnosed, surgery is the most common treatment for all stages of CRC. Tissue from the resection is tested by pathologists to detect dMMR. If resected tissue is not available, biopsy tissue can also be used. Biopsy material has been shown to be as reliable as resection specimen material in detecting a dMMR.

This treatment pathway is part of standard care in Australia, so the current management is not expected to change up to the point of referral for the service.

27. 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):

current clinical management pathway before patients are eligible for MMR IHC includes the following steps:

- Patients may initially present with symptoms to their GP (10-15% may present to the emergency department)
- Patients may also be identified via preventive screening by colonoscopy
- Tissue is obtained from colonoscopy (or surgical resection if patients have received surgery)
- Tissue (resection or biopsy) is sent to the pathology laboratory for histology/staging and molecular testing

Please refer to Attachment 1 for the current clinical algorithm and proposed algorithm

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

The IHC method uses antibodies directed against each MMR protein to detect the expression of the proteins in the tumor cells. Tests are performed on formalin-fixed paraffin-embedded tumour tissue to identify one of four MMR proteins (MLH1, MSH2, MSH6 and PMS2). Protein expression is scored positive if at least one cancer cell nucleus shows staining, negative if none of the tumour cells show staining with positive internal control, and not applicable if neither tumour nor stromal cells show protein expression. Tumours are classified as dMMR when there is an absence of at least 1 of 4 mismatch repair proteins expression.

The majority of dMMR cancers show loss of expression of both MMR proteins in a heterodimer (either MLH1/PMS2 or MSH2/MSH6) in the cancer cells, with preserved expression of the other heterodimer. In sporadic dMMR cancers, loss of MLH1/PMS2 expression is characteristic, whereas in Lynch syndrome (i.e. hereditary dMMR) either heterodimer may be lost.

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

No

30. 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

31. 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):

Patients are expected to receive one test throughout the course of their disease. Testing must be performed in an accredited laboratory by a certified pathologist. MMR testing should be requested by the treating clinician.

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

A biopsy or surgical resection is required to obtain tissue for the IHC test. These procedures are currently part of standard management for patients with CRC, so they would not present an additional burden to patients or the health system.

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

Pathologists will be responsible for undertaking the MMR IHC test. If found to be dMMR, treatment with pembrolizumab would be managed by medical oncologists.

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

No

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

Medical oncologists would be required to request the MMR IHC test for the purposes of pembrolizumab treatment.

36. 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:

IHC testing is a well-established technique in all major pathology labs. Most laboratories already perform the MMR IHC test, either routinely or based on clinician request. Testing must be performed in an accredited laboratory by a certified pathologist. Laboratories should adhere to the Royal College of Pathologists of Australasia Colorectal Cancer Structured Reporting Protocol.

37. (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

38. 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)

39. 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):

We are nominating two comparators for the co-dependent submission:

- 1) No testing + Standard of care administered to all patients
- 2) No testing + Pembrolizumab administered to all patients

40. 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

41. 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):

After initial diagnosis/staging and molecular testing, Stage IV CRC patients typically receive systemic chemotherapy. The chemotherapy drugs licensed for treatment of bowel cancer in Australia are:

- 5-FU (5-fluorouracil)
- Capecitabine (Xeloda)
- Oxaliplatin (Eloxatin)
- Irinotecan (Camptosar)
- Bevacizumab (Avastin)
- Cetuximab (Erbix) – if RAS wildtype
- Panitumumab

In Stage IV cancer, a combination of two or more drugs is common, for example:

- FOLFOX (5-FU + Oxaliplatin)
- FOLFIRI (5-FU + Irinotecan)
- Capecitabine
- Avastin + FOLFOX
- Avastin + FOLFIRI
- Cetuximab + FOLFOX (if RAS wildtype)
- Cetuximab + FOLFIRI (if RAS wildtype)

In addition to drug and drug administration cost, healthcare resources associated with treatment may include the management of drug-related toxicities, on-going disease management costs (e.g imaging, liver surgery), post-progression treatments and palliative care costs.

Please refer to Attachment 1 for the current clinical algorithm and proposed clinical algorithm.

42. (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:

Outline service/comparator substitution here

43. 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):

If patients are found to be dMMR, they would receive treatment with pembrolizumab (200 mg IV every 3 weeks). All other patients would continue to receive standard management.

It is hypothesised that treatment with pembrolizumab will delay disease progression and mortality and may have a superior safety profile. Therefore, healthcare resource utilisation in the following areas could potentially be reduced:

- Adverse event related treatment;
- Ongoing disease management resource utilisation;
- Post-progression/2L therapy; and
- Palliative care costs.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. 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):

KEYNOTE-177 in a phase III trial of pembrolizumab versus SoC chemotherapies in subjects receiving 1L treatment for stage IV MSI-H or dMMR CRC. Approximately 270 subjects will be randomized in a 1:1 ratio to receive pembrolizumab or standard of care (SOC). This is an open label study. The trial is currently on-going. Results are expected at the end of 2018.

The primary objective of the trial is:

- 1) To compare Progression Free Survival (PFS) per RECIST 1.1 by central imaging vendor.

Hypothesis 1: Pembrolizumab prolongs PFS per RECIST 1.1 by central imaging vendor compared to SOC chemotherapies.

The secondary objectives of the trial are:

- 2) To compare Overall Response Rate (ORR) per RECIST 1.1 by central imaging vendor.

Hypothesis 2: Pembrolizumab improves ORR compared to SOC chemotherapies

- 3) To compare Overall Survival (OS).

Hypothesis 3: Pembrolizumab prolongs OS compared to SOC chemotherapies.

- 4) To evaluate the safety and tolerability profiles.

Hypothesis 4: Pembrolizumab has a non-inferior safety and tolerability profile to SoC.

The clinical claims will be related to the hypotheses of the trial and are dependent upon the results of the interim/final analyses.

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

- Superiority
 Non-inferiority

46. 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:

- Serious adverse events (defined as events that result in death; are life threatening; result in persistent or significant disability/incapacity; result in or prolongs an existing inpatient hospitalization; are a congenital anomaly/birth defect; or other important medical event).
- Adverse events
- Toxicities
- Safety of the MMR IHC test (including rates of re-biopsy required for testing)

Clinical Effectiveness Outcomes:

- Diagnostic Accuracy of MMR IHC test (Sensitivity, Specificity, Positive predictive value, Negative Predictive Value). Concordance with MSI status testing
- Progression Free Survival (PFS) per RECIST 1.1
- Overall Response Rate (ORR) per RECIST 1.1
- Overall Survival
- Patient Reported Outcomes (EuroQol EQ5D-3L, EORTC QLQ-C30, and EORTC QLQ-CR29)

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

It is estimated that 17,520 cases of CRC will be diagnosed in Australia in 2016 (AIHW, 2016). Of these, approximately 10% of cases, or 1752 patients, are expected to have Stage IV cancer (Morris, 2007).

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

Patients would require only 1 test throughout the course of their disease.

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

The proposed medical service would only be required in year 1 (if the patient has not previously had a test or previous results are not available)

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

1752 patients are expected to be diagnosed with Stage IV CRC and would receive MMR IHC testing (however, some of these patients may have had MMR IHC tests performed at earlier stages of disease. As the results are not expected to change over time, these earlier results would still be relevant for Stage IV treatment). Of the Stage IV patients, approximately 4% of patients (n=70 patients) would be confirmed as having dMMR and would be treated with pembrolizumab.

51. 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:

IHC MMR testing is already routinely undertaken in CRC patients in approximately 54% of Australian laboratories (Mascarenhas, 2015). Therefore, uptake is not expected to change from current rates at these locations. The remaining laboratories screen samples based on red flag criteria (40%) or upon clinician request (6%). While uptake would increase in these laboratories, they are already performing MMR IHC testing and therefore have existing resources and referral arrangements in place.

MMR IHC results are used for other clinical-decision making purposes, so many patients will have had testing performed at earlier stages of disease. Furthermore, some centres are already practising universal testing. Therefore, 'leakage' related to the introduction of co-dependent treatment with pembrolizumab is not expected.

PART 8 – COST INFORMATION

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

The MMR IHC is currently billed to MBS item 72847 (IHC with 4-6 antibodies). The Medicare fee of \$89.40 is not expected to change.

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

Based on pathologist feedback, a typical IHC MMR test typically takes 10 minutes to perform. Results are available within a 24 hour timeframe.

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

Category 6 – Pathology Services
Proposed item descriptor: Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen (4-6 antibodies) to determine if the requirements relating to mismatch repair deficiency status for access to pembrolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled
Fee: \$89.40 Benefit: 75% = \$67.05 85% = \$76.00

PART 9 – FEEDBACK

The Department is interested in your feedback.

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

Insert approximate duration here

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

Yes

No

(b) If no, provide areas of concern:

Describe areas of concern here

57. (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

58. (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:

Insert feedback here