Application Form

(New and Amended

Requests for Public Funding)

(Version 2.4)

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires in order to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

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

Phone: +61 2 6289 7550
Fax: +61 2 6289 5540
Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: ***Redacted***

ABN: ***Redacted***

Business trading name: ***Redacted***

Primary contact name: *Redacted*

Primary contact numbers

Business: ***Redacted***

Mobile: ***Redacted*** Email: ***Redacted***

Alternative contact name: *Redacted*

Alternative contact numbers

Business: ***Redacted***

Mobile: ***Redacted***

Email: ***Redacted***

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

☐ Yes
☒ No

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

☐ Yes
☒ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. **Application title**

   Heritable mutations which increase risk in colorectal and endometrial cancer.

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)**

   Familial adenomatous polyposis (FAP), juvenile polyposis syndrome (JPS), Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer (HNPCC)), Peutz-Jeghers syndrome (PJS), hereditary mixed polyposis syndrome (HMPS) and autosomal recessive colorectal adenomatous polyposis (*MUTYH*-associated polyposis or MAP) are all inheritable syndromes predisposing to colorectal and other epithelial cancers.

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)**

   Genetic testing should be considered in patients with a personal history of colorectal or endometrial cancer with potential hereditary genetic risk of >10% as assessed by their treating specialist. This would include: CRC with evidence of mismatch repair deficiency (MMR) and/or clinical evidence of a possible familial polyposis syndrome; and cascade testing of family members of patients identified with clinically actionable pathogenic mutations on the request of a medical specialist or clinical geneticist.

   The proposed genes for testing are as follows: APC, SMAD4, BMPR1A, MLH1, MSH2, MSH6, PMS2, STK11, GREM1, MUTYH, EPCAM* [*deletions associated with epigenic silencing of MSH2]

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

   ☒ Yes
   ☐ No

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

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

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

   Not applicable.

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

   i.   ☐ An amendment to the way the service is clinically delivered under the existing item(s)
   ii.   ☐ An amendment to the patient population under the existing item(s)
   iii. ☐ An amendment to the schedule fee of the existing item(s)
   iv.   ☐ An amendment to the time and complexity of an existing item(s)
   v.   ☐ Access to an existing item(s) by a different health practitioner group
   vi.   ☐ Minor amendments to the item descriptor that does not affect how the service is delivered
   vii. ☐ An amendment to an existing specific single consultation item
   viii. ☐ An amendment to an existing global consultation item(s)
   ix.   ☐ Other (please describe below):

   Not applicable.

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

   i.   ☒ A new item which also seeks to allow access to the MBS for a specific health practitioner group

    ii.   ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)

    iii.   ☐ A new item for a specific single consultation item

    iv.   ☐ A new item for a global consultation item(s)

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

☐ Yes
☒ No

(g) If yes, please advise:

Not applicable.

7. What is the type of service:

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

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

    i.   ☐ To be used as a screening tool in asymptomatic populations

    ii.   ☒ Assists in establishing a diagnosis in symptomatic patients

    iii.   ☒ Provides information about prognosis

    iv.   ☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy

    v.   ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

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

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☒ No

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

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

Insert PBAC submission item number here

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

Trade name: Insert trade name here
Generic name: Insert generic name here

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

☐ Yes
☒ No

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

(b) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

☐ Yes
☒ No

(c) 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

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

Insert sponsor and/or manufacturer name(s) here

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

Single use consumables: Sequencing reagents
Multi-use consumables: Not applicable.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

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

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

   x Class III
   ☐ AIMD
   ☐ N/A

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

   ☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
   x 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)?

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

   ARTG listing, registration or inclusion number: Various
   TGA approved indication(s), if applicable: Insert approved indication(s) here
   TGA approved purpose(s), if applicable: Insert approved purpose(s) here

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

   ☐ Yes (please provide details below)
   ☐ No

Date of submission to TGA: 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

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

   ☐ Yes (please provide details below)
   ☐ No

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

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

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
	For each key journal article or published research relating to your proposed service, insert the type of study design in this column and columns below	Genetic testing for hereditary mutations in the mismatch repairs genes (MMR genes)	For each key journal article or published research relating to your proposed service, insert a short description of research in this column and columns below		For each key journal article or published research relating to your proposed service, insert the date of publication in this column and columns below
1	Clinical practice guidelines	Genetic Testing for Heritable Mutations in the APC Gene	Clinical guidelines for the genetic testing for heritable mutations in the APC gene	eviQ guidelines **(requires user to register and create login, pdf available if preferred)**	30 Sep 2015

	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***
2.	Clinical practice guidelines	Identification of individuals at risk for Lynch syndrome using targeted evaluations and genetic testing: National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer joint practice guideline	Guidelines for clinicians for the evaluation of patients for Lynch Syndrome	J Genet Couns. 2012;21(4):484-493.	Aug 2012
3.	Study of diagnostic accuracy	Tumor Mismatch Repair Immunohistochemistry and DNA *MLH1* Methylation Testing of Patients With Endometrial Cancer Diagnosed at Age Younger Than 60 Years Optimizes Triage for Population-Level Germline Mismatch Repair Gene Mutation Testing	Endometrial cancers from 702 patients recruited into the Australian National Endometrial Cancer Study (ANECS) were tested for MMR protein expression using immunohistochemistry (IHC) and for MLH1 gene promoter methylation in MLH1-deficient cases.	J Clin Oncol 2014;32(2):90-100.	Jan 2014

	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.	Clinical practice guidelines	Molecular testing strategies for Lynch syndrome in people with colorectal cancer	Clinical practice guidelines for molecular testing strategies for Lynch syndrome	https://www.nice.org.uk/guidance/dg27/history	Feb 2017
5.	Study of diagnostic accuracy	Population-based screening for Lynch Syndrome in Western Australia	Results of screening for LS in Western Australia (WA) during 1994-2012.	Int J Cancer. 2014;135(5):1085-91.	29 Jan 2014
6.	Study of diagnostic accuracy	Application of a 5-tiered scheme for standardized classification of 2,360 unique mismatch repair gene variants in the InSiGHT locus-specific database	Collaborative study by International Society for Gastrointestinal Hereditary Tumours (InSiGHT) to develop a standardised classification scheme for LS associated genes.	Nat Genet. 2014;46(2):107-15.	Feb 2014
7.	Literature review	Integrating personalised genomics into risk stratification models of population screening for colorectal cancer	Review of literature relating to colorectal cancer including genetic risk stratification for CRC screening in younger individuals not included in the NBCSP.	Aust N Z J Public Health. 2017;41(1):3-4.	2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
8.	Study of diagnostic accuracy	Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer	Study of families of 5,744 colorectal cancer cases (probands) recruited from population cancer registries in the USA, Canada and Australia and screened probands for mutations in mismatch repair genes and MUTYH. Results found that 1 in 279 of the population carry mutations in mismatch repair genes (MLH1= 1 in 1946, MSH2= 1 in 2841, MSH6= 1 in 758, PMS2= 1 in 714), 1 in 45 carry mutations in MUTYH, and 1 in 504 carry mutations associated with an average 31-fold increased risk of colorectal cancer in unidentified major genes.	[Cancer Epidemiol Biomarkers Prev. 2017;26(3):404-12.](#)	Mar 2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
9	Study of diagnostic accuracy	Tumour testing to identify lynch syndrome in two Australian colorectal cancer cohorts	Study to identify MMR gene mutation carriers in two cohorts of population-based CRC utilising a combination of tumour and germline testing approaches. CRCs from 813 patients diagnosed with CRC <60 years of age from the Australasian Colorectal Cancer Family Registry (ACCFR) and from 826 patients from the Melbourne Collaborative Cohort Study (MCCS) were tested for MMR protein expression using immunohistochemistry (IHC), microsatellite instability (MSI), BRAFV600E somatic mutation and for MLH1 methylation. MMR gene mutation testing (Sanger sequencing and MLPA) was performed on germline DNA of patients with MMR-deficient tumours and a subset of MMR-proficient CRCs.	J Gastroenterol Hepatol, 2017;32(2):427-38.	21 Feb 2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
10.	Clinical practice guidelines	Familial colorectal cancer syndromes: an overview of clinical management	Summary of the most common familial CRC syndromes and their medical and surgical management, with specific emphasis on evidence-based interventions that improve patient outcome.	Expert Rev Gastroenterol Hepatol 2015;9:757-64	16 Mar 2015
11.	Observational study	Cancer risks for MLH1 and MSH2 mutation carriers	Study of 17,576 members of 166 MLH1 and 224 MSH2 mutation-carrying families from the Colon Cancer Family Registry in Australia. Results demonstrated the average CRC cumulative risks at the age of 70 years (95% confidence intervals) for MLH1 and MSH2 mutation carriers, respectively, were estimated to be 34% and 47% for male carriers and 36% and 37% for female carriers. Corresponding EC risks were 18% and 30%.	Hum Mutat. 2013;34(3):490-7.	Mar 2013

	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***
12.	Clinical Practice Guidelines	Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. Australian Cancer Network Colorectal Cancer Guidelines Revision Committee.	Clinical Practice Guidelines for Colorectal Cancer	Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer	8 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***
13.	Observational study	Risks of Lynch Syndrome Cancers for *MSH6* Mutation Carriers	Study of 113 families of MSH6 mutation carriers from five countries through family cancer clinics and population-based cancer registries. Results demonstrated that for MSH6 mutation carriers, the estimated cumulative risks to ages 70 and 80 years, respectively, were as follows: for colorectal cancer, 22% and 44% for men and 10% and 20% for women; for endometrial cancer, 26% and 44%; and for any cancer associated with Lynch syndrome, 24% and 47% for men and 40% and 65% for women. Compared with incidence for the general population, MSH6 mutation carriers had an eightfold increased incidence of colorectal cancer (HR = 7.6, which was independent of sex and age. Women who were MSH6 mutation carriers had a 26-fold increased incidence of endometrial cancer (HR = 25.5) and a sixfold increased incidence of other cancers associated with Lynch syndrome (HR = 6.0).	J Natl Cancer Inst. 2010;102(3):193-201.	3 Feb 2010

	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***
14.	Observational study	The clinical phenotype of Lynch syndrome due to germline *PMS2* mutations	PMS2 mutation analysis using long range PCR and MLPA for 99 probands diagnosed with Lynch syndrome-associated tumors showing isolated loss of PMS2 by immunohistochemistry. Results demonstrated that PMS2 mutations contribute significantly to Lynch syndrome but the penetrance for monoallelic mutation carriers appears to be lower than that for the other mismatch repair genes.	Gastroenterology. 2008;135(2):419-28.	Aug 2008
15.	Observational study	Cancer Risks Associated With Germline Mutations in *MLH1*, *MSH2*, and *MSH6* Genes in Lynch Syndrome	Families with Lynch syndrome from 40 French cancer genetics clinics participating in the ERISCAM (study; 537 families with segregating mutated genes (248 with MLH1; 256 with MSH2; and 33 with MSH6) were analysed for age-specific cumulative cancer risks.	JAMA. 2011;305(22):2304-10	8 Jun 2011

	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***
16.	Observational study	Lynch Syndrome Caused by Germline PMS2 Mutations: Delineating the Cancer Risk	European study of cancer risk for PMS2 mutation carriers from 98 PMS2 families from family cancer clinics, a total of 2,548 family members and 377 proven mutation carriers. The cumulative risk (CR) of CRC for male mutation carriers by age 70 years was 19%. The CR among female carriers was 11% for CRC and 12% for EC. The mean age of CRC development was 52 years, and there was a significant difference in mean age of CRC between the probands (mean, 47 years) and other family members with a PMS2 mutation (mean, 58 years, P < .001). Significant Standardized incidence ratios (SIRs) were observed for cancers of the small bowel, ovaries, breast, and renal pelvis.	J Clin Oncol. 2015;33(4):319-25.	4 Feb 2015

	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***
17.	Observational study	Colorectal and Other Cancer Risks for Carriers and Noncarriers From Families With a DNA Mismatch Repair Gene Mutation: A Prospective Cohort Study	Study to determine cancer risks for carriers and non carriers from families with a MMR gene mutation a cohort of 446 unaffected carriers of an MMR gene mutation (MLH1, n = 161; MSH2, n = 222; MSH6, n = 47; and PMS2, n = 16) and 1,029 their unaffected relatives who did not carry a mutation every 5 years at recruitment centres of the Colon Cancer Family Registry.	J Clin Oncol. 2012;30(9):958-64.	13 Feb 2012

	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***
18.	Observational study	Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database	Multicentre study of patients carrying Lynch syndrome-associated mutations affecting MLH1, MSH2, MSH6 or PMS2. 1942 mutation carriers without previous cancer had follow-up including colonoscopic surveillance for 13 782 observation years. 314 patients developed cancer. Among first cancer detected in each patient the colorectal cancer cumulative incidences at 70 years by gene were 46%, 35%, 20% and 10% for MLH1, MSH2, MSH6 and PMS2 mutation carriers, respectively. The equivalent cumulative incidences for endometrial cancer were 34%, 51%, 49% and 24%; and for ovarian cancer 11%, 15%, 0% and 0%.	Gut. 2017;66(3):464-72.	2017
19.	Observational study	Colorectal surveillance in Lynch syndrome families	Report on surveillance program for registered LS families.	Cancer. 2013;12(2):261-5.	23 Mar 2013

	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***
20.	Cost benefit study	A model-based assessment of the cost–utility of strategies to identify Lynch syndrome in early-onset colorectal cancer patients	Study of the cost–utility of strategies to identify Lynch syndrome in individuals with early-onset colorectal cancer in the UK National Health Service.	BMC Cancer. 2015;15(1):313.	25 Apr 2015
21.	Clinical practice guidelines	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	Clinical practice guidelines for the evaluation of CRC.	J of Clinl Oncol. JCO.2016.71.9807,2016;.71.9807.	May 2017
22.	Letter to the Editor	Universal screening for microsatellite instability in colorectal cancer in the clinical genomics era: new recommendations, methods, and considerations	Discussion of Clinical Practice Guidelines for testing of MMR MSI with summary of advantages and drawbacks of different conventional and NGS based methods for testing.	Fam Cancer. 2017;16(4):525–9.	12 Apr 2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
23.	Report	Misdiagnosed, misunderstood and missing out: Lynch syndrome Australia's untold health story. Lynch Syndrome Australia.	Report by Lynch Syndrome Australia into health system issues for patients with Lynch Syndrome with recommendations for improvements.	Lynch Syndrome Australia. Misdiagnosed, misunderstood and missing out: Lynch syndrome Australia's untold health story	2017

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

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

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

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

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

	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***
11.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
12.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
13.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
14.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
15.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date

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

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

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

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

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

    Royal College of Pathologists of Australasia (RCPA)

20. **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 Incorporated (MOGA), and the Clinical Oncology Society of Australia.

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

    Human Genetics Society of Australasia (HGSA)

    Genetic and Rare Disease Network (GaRDN)

    Genetic Alliance Australia

    Bowel Cancer Australia

    Lynch Syndrome Australia

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

    Not applicable

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

    Name of expert 1: *Redacted*

    Telephone number(s): *Redacted*

    Email address: *Redacted*

    Justification of expertise: *Redacted*

    Name of expert 2: *Redacted*

    Telephone number(s): *Redacted*

    Email address: *Redacted*

    Justification of expertise: *Redacted*

    Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

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

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. **Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:**

Familial adenomatous polyposis (FAP), juvenile polyposis syndrome (JPS), Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer (HNPCC)), Peutz-Jeghers syndrome (PJS), hereditary mixed polyposis syndrome (HMPS) and autosomal recessive colorectal adenomatous polyposis (*MUTYH*-associated polyposis or MAP) are all inheritable syndromes predisposing to colorectal and other epithelial cancers.

The risk of colorectal cancer is elevated for carriers of the listed gene mutations. The level of risk, variation with age of first colorectal cancer diagnosis, and variation between carriers of mutations in the listed genes has been confirmed in prospective studies and a meta-analysis of published data.

A 15 year study of screening for colorectal cancer in patients with HNPCC (Jarvinen, 2000) showed that colorectal cancer developed in 8 (6%) of 133 in the study group compared with 19 (16%) of 119 in the control group (p=0.014). The relative risk of CRC was 0.377 (95% confidence interval [CI], 0.171–0.829) in the study group vs. controls, corresponding to a reduction of 62% (95% CI, 17%–83%).

The corresponding relative CRC risk of the screened mutation positive individuals was 0.440 (95% CI, 0.215–0.900) and the reduction due to screening 56% (95% CI, 10%–79%). The cumulative proportions of CRC-free subjects were significantly higher in the study group than control group both when all subjects (p= 5 0.019) and when mutation-positive subjects alone (P 5 0.034) were included. Also, the stage distribution of the CRCs in the study subjects was significantly more favourable than that in the control group.

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

Heritable colorectal and endometrial cancer genetic testing should be considered in an individual:

- with a personal history of colorectal or endometrial cancer with potential hereditary genetic risk; OR
- clinical evidence of a possible familial polyposis syndrome; OR
- who falls into one or more of the following specific categories:

Colorectal cancer (CRC) with evidence of mismatch repair deficiency (MMR):

- o Germline MMR mutations
- o Loss of expression by immunohistochemistry (IHC)
- o Microsatellite instability (MSI)

Familial polyposis syndrome

- o More than 100 adenomatous polyps
- o Between 20 and 100 adenomatous polyps
- o Extra colonic manifestations (when colorectal polyp status is unknown)
- o Multiple osteomas of the skull or mandible
- o 10 or more adenomas diagnosed age < 50 years old
- o Multiple CRCs with or without synchronous adenomas
- o Intraabdominal or abdominal wall desmoid tumour diagnosed at age 10-60 yrs
- o Desmoid tumour (any location) diagnosed age <10 yrs
- o Multiple and/or bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE) at any age
- o Synchronous CRC cancers (suggestive of MAP)

- o   Clinical evidence suggestive of hamartomatous polyposis syndrome
- o   Clinical evidence suggestive of Peutz-Jeghers syndrome

A specialist will first see these patients as inpatients or in a clinic by referral from a general practitioner. After a clinical assessment, consultation will occur with a clinical geneticists / genetic counsellor with expertise in genetic counselling. The delivery of results to the patients and / or family would require a formal consultation with the specialist, and clinical geneticist / genetic counsellor.

A hereditary cancer clinic and family cancer centres would be appropriate gatekeepers for predictive testing and interpretation of results for family members of a proband.

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

The proposed intervention is already offered in the healthcare system, however, the current pathway is:

- for the gastrointestinal (GI) cancer predisposition genes, those testing positive require close surveillance with colonoscopy to detect the rapidly growing cancers which occur driven by, for example, the mutator phenotype (accumulating hundreds of mutations in the tumours) typically of Lynch Syndrome;
- for those who do develop colorectal cancer are usually advised to have extensive rather than limited, oncological resections, to reduce their risk of metachronous cancer;
- for those family members testing negative for the family specific mutation need no special surveillance and, if otherwise of average risk, can join the iFOBT-based National Bowel Cancer Screening Program. If other factors place them at higher than average risk, they should be managed as appropriate for that circumstance.

If genetic testing has not been undertaken, all family members would need to remain under colonoscopic surveillance in case they had inherited the family specific mutation in the relevant gene. Colonoscopy in this setting has been shown to reduce mortality, at least in comparison with a control group who did not agree to colonoscopy (not randomised) (Jarvinen, 2000). There are large cost savings to the healthcare system by segregating family members in this way. Currently, this process takes place in the Familial Cancer Clinics nationwide.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

The key components and clinical steps is described as above.

Once the request has been made, the patient would be required to provide a blood sample. The samples analysed are most commonly blood samples from affected individuals except in the case of cascade testing where duplicate and independent blood samples from affected and/or unaffected family members are submitted for specific analysis. In situations where a blood sample from an affected person in a high risk family is unavailable, tissue samples from deceased individuals may be provided.

Genetic risk assessment will follow classical Mendelian inheritance patterns.

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

No.

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

No.

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

Once off diagnostic test.

31. **If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:**

Consultation with clinical geneticists / genetic counsellor with expertise in genetic counselling. The delivery of results to the patients and / or family would require a formal consultation with the specialist, and clinical geneticist / genetic counsellor.

Hereditary cancer clinic and family cancer centres would be appropriate gatekeepers for predictive testing and interpretation of results for family members of a proband.

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

An oncologist would be required to request the service.

A pathologist would perform the service and provide the clinical report that would include interpretation of the results.

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

No.

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

Consideration should be given to restricting this service to a specialised setting.

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

Only oncologists would request the service and an appropriately qualified pathology to provide the service.

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

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

Specify further details here

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

Not applicable.

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

☒ Yes
☐ No – please specify below

Specify further details here

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

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

No testing.

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

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

40. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):

Given the risk of colorectal cancer is elevated for carriers of the listed gene mutations the altered clinical pathways as a consequence of testing positive, or reciprocally, negative for a pathogenic mutation in one of the actionable genes is summarised in the table below. Generally for the gastrointestinal (GI) cancer predisposition genes, those testing positive require close surveillance with colonoscopy to detect the rapidly growing cancers which occur driven by, for example, the mutator phenotype (accumulating hundreds of mutations in the tumours) typically of Lynch Syndrome.

Those who do develop colorectal cancer are usually advised to have extensive rather than limited, oncological resections, to reduce their risk of metachronous cancer. On the other hand, those family members testing negative for the family specific mutation need no special surveillance and, if otherwise of average risk, can join the iFOBT-based National Bowel Cancer Screening Program. If other factors place them at higher than average risk, they should be managed as appropriate for that circumstance.

If genetic testing has not been undertaken, all family members would need to remain under colonoscopic surveillance in case they had inherited the family specific mutation in the relevant gene. Colonoscopy in this setting has been shown to reduce mortality, at least in comparison with a control group who did not agree to colonoscopy (not randomised) (Jarvinen, 2000). There are large cost savings to the healthcare system by segregating family members in this way. Currently, this process takes place in the Familial Cancer Clinics nationwide.

Lynch syndrome:

Colorectal

	Mutation Positive	Mutation Negative
Surgical	• consider subtotal colectomy in selected individuals	• not applicable
Surveillance MSH6/PMS2	• annual colonoscopy from age 30 years or 5 years younger than youngest affected if <35 years • review frequency of colonoscopy at age 60 years with a view to reduced frequency	• general population screening
Surveillance MLH1/MSH2	• annual colonoscopy from age 25 years or 5 years younger than youngest affected if <30 years • review frequency of colonoscopy at age 60 years with a view to second yearly frequency	
Risk reducing Medication	• aspirin is recommended for risk reduction	• not applicable

Endometrial

	Mutation Positive	Mutation Negative
Surgical	• recommend hysterectomy after childbearing complete or from age 40 years, or 5 years younger than the youngest affected, whichever comes first • pros and cons of surgery should be discussed with the patient	• no surgery

Ovarian

	Mutation Positive	Mutation Negative
Surgical	• RRSO at time of hysterectomy • recommend hormone replacement therapy (HRT) at the time of RRSO and continue until the usual time of menopause	• no surgery

Gastric

	Mutation Positive	Mutation Negative
Surveillance	• consider second yearly gastroscopy from age 30 years in families with gastric cancer or those at high ethnic risk e.g. Chinese, Korean, Chilean and Japanese	• no surveillance

Familial adenomatous polyposis

Colorectal

	Mutation Positive	**Mutation Negative**
Surgical	• colectomy is standard of care and is strongly recommended • timing of surgery: typically late teens, exact timing to be determined by patient and number of polyps present	• no surgery
Surveillance	• prior to colectomy: From age 1015yrs (usually), annual colonoscopy (flexible sigmoidoscopy if colonoscopy contraindicated or unavailable) • annual surveillance of residual rectum or ileal pouch is required following colectomy	• no surveillance

Duodenum or periampulla

	Mutation Positive	**Mutation Negative**
Surgical	• consider duodenectomy for Stage IV adenomas	• no surgery
Surveillance	• from age 25: Upper gastrointestinal endoscopy frequency dependent on Spigelman criteria	• no surveillance

In summary, disease management of mutation positive family members would follow the above recommendations. Mutation negative family members would revert to general population risk and follow guidelines for screening of the general population.

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

☒ Yes
☐ No

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

Some investigations will still be required for clinical management of proband patients.

Disease management of mutation positive family members would follow the above recommendations. Mutation negative family members would revert to general population risk and follow guidelines for screening of the general population.

42. **Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):**

The new medical service would improve the identification of persons at risk of developing colorectal and endometrial cancer and allow for appropriate advice for the prevention of disease. There will be increased numbers of patients requiring early surgical intervention and entering surveillance programs with a decrease in patients requiring later stage surgical treatment and chemotherapy. There will also be a decrease in the number of unnecessary referrals as approximately half of the targeted population will have no increase in their risk of disease by virtue of not carrying the disease causing genetic variant. The medical service is expected to reduce the incidence, morbidity and mortality of these cancers.

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

In broad terms, the following benefits are expected through offering the proposed gene testing (primarily the benefits to mutation positive family members are summarised here). Evidence to back up these claims will be subsequently presented to MSAC for their consideration

Lynch syndrome:

Colorectal

- Increased life expectancy
- Significant reduction of bowel cancer risk equivalent to general population risk through more intensive surveillance

Endometrial and Ovarian

- Hysterectomy and recommend risk reducing salpingo-oophorectomy (RRSO) are interventions which significantly reduce the risk of both endometrial and ovarian cancer

Familial adenomatous polyposis

- Systematic reviews have found that registration in dedicated registers, surveillance and colectomy have a consistent and significant reduction in incidence and CRC related mortality

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

☒ Superiority
☐ Non-inferiority

45. **Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:**

Safety Outcomes: Consideration of the relative safety of performing the proposed gene testing versus the main comparator will primarily focus on the presentation of 'flow on' safety consequences that arise as a result of conducting the proposed service. It will not consider the immediate or delayed safety consequences of physically performing the service given the low risk nature of the blood collection to obtain a sample to conduct the test. **Clinical Effectiveness Outcomes:** Clinical effectiveness outcomes will be presented through a clinical utility construct as per the CUC proforma including presentation of analytical validity and clinical validity data as well as change in management/overall outcome data (survival etc)

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

    Lynch syndrome

    The frequency of germline mutations in a MMR gene in unselected individuals with colorectal cancers is 2-4%. The frequency of germline mutations in MMR gene in unselected individuals with endometrial cancers is ~3%. De novo mutations in the MMR genes are very rare.

    FAP

    Prevalence in colorectal cancer patients ~1%

    The frequency of APC germline mutations in unselected individuals with CRC is <0.2%

    MUTYH

    The frequency of biallelic MUTYH mutations in unselected individuals is 1-2 per 10,000.

    The frequency of monoallelic MUTYH mutations in unselected individuals is 1-2%.

    The likelihood of detecting biallelic MUTYH mutations in an individual with polyposis increases if the family history is suggestive of autosomal recessive inheritance, i.e. parental consanguinity or a sibling/s with documented polyposis or colorectal cancer.

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

    Once only

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

    Not relevant as the test is once only.

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

    Approx. 800, a significant proportion would be predictive testing of relatives.

    This estimate is calculated from an extrapolation of NSW statistics, where there are projected to be 6000 CRC cancers diagnosed per year; <1% will be due to FAP and <3% Lynch Syndrome.

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

    Uptake in the next three years will result in all of the at risk population using the test in diagnosis.

    It is estimated that the number of patients utilising the test will remain at less than 900 in three years' time.

    Leakage to populations not targeted by the service would be restricted by the item descriptor.

PART 8 – COST INFORMATION

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

    Diagnostic genetic testing of affected individuals

    Proposed MBS fee(s): $1200

    Predictive genetic testing of family members

    Proposed MBS fee(s): $400

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

    A turnaround time of twenty working days is required for the complete testing process from specimen collection to pathology report.

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

Category MBS Pathology Table Category 6, Group P7 -Genetics
Characterisation of germline gene variants in three or more of the following genes APC, MLH1, MSH2, MSH6, PMS2, MUTYH with or without any of these genes SMAD4, BMPR1A, STK11, GREM1, and EPCAM* [*deletions associated with epigenic silencing of MSH2], in a patient with colorectal or endometrial cancer, or familial polyposis syndrome, for whom clinical and family history criteria, as assessed by a treating specialist place the patient at >10% risk of having a clinically actionable pathogenic mutation identified. Fee: $1,200

Category MBS Pathology Table Category 6, Group P7 -Genetics
Request by a clinical geneticist, or a medical specialist providing professional genetic counselling services, for the detection of a clinically actionable pathogenic mutation previously identified in a gene listed in Item XXXX in a relative Fee: $400