Australian Government

Department of Health

MSAC Application 1668

Whole body magnetic resonance imaging for detection of cancer in individuals with germline pathogenic TP53 variants

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.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation name: Australian Genomic Cancer Medicine Centre Ltd
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?

N/A

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Whole body magnetic resonance imaging (WBMRI) for detection of cancer in individuals with germline pathogenic *TP53* variants.

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)

Li Fraumeni Syndrome (LFS) is an ultra-rare condition (between 1/5000-1/20,000 of the population) associated with a very high risk of cancers in multiple tissues. LFS is caused by germline pathogenic variants in the *TP53* gene. The estimated risk of cancer by age 30 years is 50%, and the lifetime cancer risk approaches 90% for men, and 100% for women. Life expectancy is severely reduced and estimated to be below 40 years of age. The most common cancer types seen in LFS are (in descending order of frequency): breast cancer, sarcomas, brain cancers, adrenocortical carcinoma, but the incidence of almost all cancer types is increased in this population. Most of these cancers are curable if detected early.

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

The proposed medical service is annual WBMRI for individuals with germline pathogenic *TP53* variants (Li Fraumeni Syndrome). Recent data from multiple groups indicates that WBMRI performed without contrast enables the detection of curable cancers in 1 in 10 individuals with germline pathogenic *TP53* variants. According to clinical practice guidelines nationally and internationally, optimal clinical management of individuals with germline pathogenic *TP53* variants (Li Fraumeni Syndrome) now requires consideration of annual WBMRI.

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

☒ Yes
☐ No

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

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

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

N/A

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

N/A

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

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

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

☐ Yes
☒ No

(g) If yes, please advise:

N/A

7. What is the type of service:

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

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

i. ☒ To be used as a screening tool in asymptomatic populations
ii. ☐ Assists in establishing a diagnosis in symptomatic patients
iii. ☐ Provides information about prognosis
iv. ☐ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

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

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

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

☐ Yes
☒ No

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

N/A

(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

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

N/A

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

☐ Yes
☒ No

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

N/A

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

☐ Yes
☒ No

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

☐ Yes
☒ No

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

N/A

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

N/A

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: Not applicable.
Manufacturer's name: Not applicable.
Sponsor's name: Not applicable.

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

☐ Class III
☐ AIMD
☒ N/A

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

N/A

(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)?

N/A

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

N/A

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

N/A

PART 4 – SUMMARY OF EVIDENCE

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

	Type of study design	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)**	**Website link to journal article or research (if available)**	**Date of publication**
1.	Observational study	Whole body magnetic resonance imaging of Li-Fraumeni syndrome patients: observations from a two rounds screening of Brazilian patients	Clinical evaluation of annual whole body magnetic resonance imaging (two rounds) in Li-Fraumeni syndrome in 59 patients, aged 2-71 years in Brazil	https://www.ncbi.nlm.nih.gov/pubmed/30107858	2018
2.	Observational study	Surveillance in germline *TP53* mutation carriers utilizing whole body magnetic resonance imaging	Clinical evaluation of baseline whole body magnetic resonance imaging in 30 *TP53* mutation carriers aged 18-62 years in Australia	https://jamanetwork.com/journals/jamaoncology/fullarticle/2646795 https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=364879&isReview=true	2017
3.	Meta-analysis	Baseline surveillance in Li-Fraumeni syndrome using whole body magnetic resonance imaging: A Meta-analysis	A meta-analysis of clinical findings from baseline whole body magnetic resonance imaging in 578 *TP53* mutation carriers, mean age 33 years, from 13 cohorts in 6 countries.	https://jamanetwork.com/journals/jamaoncology/fullarticle/2646798	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
4.	Observational study	Whole body magnetic resonance imaging and brain MRI baseline surveillance in TP53 germline mutation carriers: experience from the Li-Fraumeni Syndrome Education and Early Detection (LEAD) clinic	Clinical evaluation of baseline whole body magnetic resonance imaging (53 scans) and brain magnetic resonance imaging (35 scans) in *TP53* mutation carriers of all ages.	https://link.springer.com/article/10.1007/s10689-017-0034-6	2017
5.	Observational study	Prevalence of cancer at baseline screening in the National Cancer Institute Li-Fraumeni Syndrome Cohort	Clinical evaluation of baseline screening including whole body magnetic resonance imaging in 116 *TP53* mutation carriers aged 3-68 years in the USA.	https://jamanetwork.com/journals/jamaoncology/fullarticle/2646797 https://clinicaltrials.gov/ct2/show/NCT01443468	2017
6.	Psychosocial study	Psychosocial morbidity in TP53 mutation carriers: is whole body cancer screening beneficial?	Mixed methods assessment of psychosocial impact of undertaking whole body magnetic resonance imaging in 17 *TP53* mutation carriers aged 18-70 years in Australia.	https://link.springer.com/article/10.1007%2Fs10689-016-9964-7	2017
7.	Observational study	Screening with whole-body magnetic resonance imaging in pediatric subjects with Li-Fraumeni syndrome: A single institution pilot study	Clinical evaluation of whole body magnetic resonance imaging in 20 paediatric *TP53* mutation carriers over 5 years in the USA	https://onlinelibrary.wiley.com/doi/full/10.1002/pbc.26822 https://clinicaltrials.gov/ct2/show/NCT02950987	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
8.	Observational study	Surveillance of Dutch patients with L-Fraumeni Syndrome: the LiFe-Guard Study	Clinical evaluation of baseline whole body magnetic resonance imaging in 56 adult *TP53* mutation carriers in the Netherlands.	https://jamanetwork.com/journals/jamaoncology/fullarticle/2646794	2017
9.	Observational study	Baseline results from the UK SIGNIFY study: a whole-body MRI screening study in TP53 mutation carriers and matched controls	Clinical evaluation of baseline whole body magnetic resonance imaging in 44 adult *TP53* mutation carriers compared to 44 population controls in the UK.	https://link.springer.com/article/10.1007/s10689-017-9965-1	2017
10.	Observational study	Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study	Clinical evaluation of a surveillance protocol including annual whole body magnetic resonance imaging in 18 *TP53* mutation carriers (children and adults) with a median follow up of 24 months.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(11)70119-X/fulltext	2011
11.	Observational study	Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study	Clinical evaluation of a surveillance protocol including annual whole body magnetic resonance imaging in 59 *TP53* mutation carriers (children and adults) with a median follow up of 32 months.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(16)30249-2/fulltext	2016 Follow up study of publication number 11 in this list

	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.	Randomized study	Lung Adenocarcinoma as part of the Li-Fraumeni Syndrome Spectrum: Preliminary data of the LIFSCREEN Randomized Clinical Trial	Preliminary evaluation of whole body magnetic resonance imaging in 107 *TP53* mutation carriers (children and adults) in France	https://jamanetwork.com/journals/jamaoncology/fullarticle/2646796 https://clinicaltrials.gov/ct2/show/NCT01464086	2017
13.	Psychosocial study	The psychosocial effects of the Li-Fraumeni Education and Early Detection program on individuals with Li-Fraumeni syndrome	Qualitative assessment of psychosocial impact of undertaking whole body magnetic resonance imaging in 20 *TP53* mutation carriers aged 18-61 years in the USA.	https://www.nature.com/articles/gim20178	2017
14.	Observational study	Diagnostic performance of whole-body NRI as a tool for cancer screening in children with genetic cancer-predisposing conditions	Clinical evaluation of whole body magnetic resonance imaging in 24 TP53 mutation carriers (aged 2-18 years) over a 5 year period.	https://www.ajronline.org/doi/full/10.2214/AJR.14.13663	2015
15.	Psychosocial study	Couples coping with screening burden and diagnostic uncertainty in Li-Fraumeni syndrome: Connection versus independence	Qualitative assessment of psychosocial impact on 26 couples of living with Li-Fraumeni syndrome including participation in whole body magnetic resonance imaging in the USA.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6584025/	2018
16.	Psychosocial study	Psychosocial effects of whole-body MRI screening in adult high-risk pathogenic TP53 mutation carriers: a case-controlled study (SIGNIFY)	Quantitative assessment of psychosocial impact of whole body MRI in 44 adult *TP53* mutation carriers and 44 matched population controls	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7146942/	2019

	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.	Protocol paper	Whole-body MRI within a surveillance program for carriers with clinically actionable germline TP53 variants – the Swedish constitutional TP53 study SWEP53	Description of a Swedish registry of *TP53* mutation carriers (41 adults and 11 children) with three optional parts including biobanking, surveillance including whole body MRI and a psychosocial study	https://pubmed.ncbi.nlm.nih.gov/31956380/	2020

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.*

None identified

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 Australian and New Zealand College of Radiologists

    Clinical Oncology Society of Australia Family Cancer Group & Human Genetics Society of Australasia Cancer Special Interest Group

    Directors of Cancer Clinical Genetics Services

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

    No comparator service

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

    Rare Cancers Australia

    Li Fraumeni Syndrome Association (Australia & NZ)

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

    Siemens, Phillips, GE, Canon are all manufacturers of instrumentation capable of WBMRI.

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:

Carriers of germline pathogenic *TP53* variants are characterised by an early age of onset of several different cancer types and an extremely high lifetime cancer risk. By age 30 years there is a 50% risk of cancer and the lifetime cancer risk is approximately 90% for males and 100% for females. From the IARC *TP53* database, the most frequent cancers observed are breast cancers (28%), soft tissue sarcomas (14%), brain tumours (13%), osteosarcomas (9%) and adrenocortical tumours (11%) with many other cancer types also observed including colorectal, lung, melanoma, ovary and haematological malignancies. Adrenocortical carcinomas occur mostly in young children and osteosarcomas are diagnosed mainly in adolescents and young adults. Brain tumours and soft tissue sarcomas occur often in children <5 years of age with a second peak in incidence in individuals aged 20-40 years. Breast cancer commonly occurs 20-40 years of age. Many other cancers types are observed also occurring at ages much younger than the general population. Carriers of germline pathogenic *TP53* variants are also at increased risk of subsequent cancer diagnoses. In 89 individuals with germline pathogenic *TP53* variants, the five year overall survival rate was 89% for those undergoing surveillance (40 individuals) and 60% for the non-surveillance group (49 individuals). The median age at death in the non-surveillance group was 23 years (range 1-59 years). There have been no formal studies evaluating life expectancy but with the early onset of cancers and poor survival it is estimated to be on average below 40 years of age.

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:

Individuals with germline pathogenic *TP53* variants are proposed to be eligible for the proposed medical service. Individuals are typically found to harbour germline pathogenic *TP53* variants within the context of a family cancer or genetics clinic, and will have genetic testing as part of the risk assessment and management process. Referral by oncologists and other health professionals to the family cancer or genetics clinic is typically based on a family member with an early age at diagnosis of an LFS spectrum cancer (breast cancer, sarcoma, brain tumour, adrenocortical carcinoma) as well as having a family history of cancer. Eligibility for genetic testing assessed within the family cancer or genetics clinic is generally based on meeting the Chompret criteria*. After genetic testing, individuals receive a clinically-accredited report confirming both the specific genetic variant (if detected), and stating that this variant is considered to be pathogenic or likely pathogenic using conventional criteria, typically on the basis of reference databases (such as IARC and Clinvar), or on the basis of the nature of the mutation (novel nonsense variants). These individuals are appropriately counselled regarding lifetime risk of cancer, current risk management guidelines and potential risk for other family members.

At this point individuals would be considered eligible for the currently proposed medical service.

*Chompret criteria (Bougeard et al., Journal of Clinical Oncology 2015)
A proband with a tumour belonging to the LFS tumour spectrum before the age of 46 years AND at least one first or second degree relative with an LFS tumour (except breast cancer) before the age of 56 years or with multiple tumours OR a proband with multiple tumours (except multiple breast tumours) two of which belong to the LFS tumour spectrum and the first of which occurred before the age of 46 years OR a proband diagnosed with adrenocortical carcinoma, choroid plexus tumour, embryonal anaplastic rhabdomyosarcoma, irrespective of family history OR a proband with breast diagnosed before the age 31 years

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 current clinical management pathway can be summarised as follows (see attachment 1)

- An individual is diagnosed with an LFS spectrum cancer (early onset breast cancer, sarcoma, brain tumour, adrenocortical carcinoma) at an early age or a family member is identified as being at risk
- Individual/family is referred to a family cancer or genetics clinic by an oncologist or other health professional
- Family cancer/genetics clinic assesses eligibility for genetic testing of the *TP53* gene using the Chompret criteria
- If eligibility for testing is established, then genetic testing is undertaken by an accredited molecular pathology service and a clinical diagnostic report generated.
- If a germline pathogenic or likely pathogenic variant in the *TP53* gene is detected in the individual then the family cancer/genetics clinic will offer counselling regarding lifetime cancer risks, potential risk for biological family members and cancer risk management guidelines.

The eviQ cancer risk management guidelines for adults with germline *TP53* mutations currently include the following recommendations:

1. Annual clinical review and physical examination
2. Avoid environmental or behavioural risks (sun, smoking, unnecessary radiation exposure)
3. Offer prophylactic mastectomy for women under 50 years
4. Annual breast MRI from age 20 years
5. Offer risk reducing medication for breast cancer
6. Consider 2-5 yearly colonoscopy from age 20 years
7. Consider 2-5 yearly endoscopy from age 25 years
8. Consider annual brain MRI
9. Consider **annual WBMRI**

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

The service would be provided only in the context of a family cancer/genetics clinic, and be ordered by an appropriately trained clinician, expert in the management of hereditary cancers. It would apply only to individuals who are carriers of pathogenic or likely pathogenic germline *TP53* variants, where the diagnosis was confirmed by an accredited molecular pathology laboratory.

The service will consist of an annual, non-contrast whole body MRI scan, which would be read by an appropriately skilled and trained radiologist.

The scan will yield 3 potential outcomes:

a) no suspicious lesions (~60%);

b) a lesion which requires either additional imaging or more frequent surveillance (~30%) or

c) a lesion(s) necessitating biopsy to confirm malignancy (~10%)

The service would form part of the routine management of carriers of pathogenic germline *TP53* variants, along with the other items listed in eviQ risk management guidelines in Q26.

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?

Not applicable.

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

The WBMRI should be performed not more frequently than annually.

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:

None.

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

Suitably qualified clinical geneticists working in appropriate familial cancer/genetic clinics will order the service and suitably qualified radiologists will deliver the service.

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

Not applicable. The service should be provided by an experienced, suitably qualified and trained radiologist.

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

Because of the complex nature of the hereditary condition, its rarity, and the challenges in reporting, it is arguable the service should be ordered only by qualified clinicians within a familial cancer or genetics clinic, and the service should be provided by a specialist radiology centre affiliated with a familial cancer or genetics clinic.

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:

Clinical geneticists who have appropriate post-graduate expertise in hereditary cancer; radiologists with appropriate expertise and training with MRI, as defined by the RANZCR.

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

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

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

Patients may be identified while an inpatient or outpatient, and in either a private or public setting. It is unlikely that the decision to perform a WBMRI scan would occur outside of these settings.

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

- ☒ Yes
- ☐ No

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):

Cancer risk management in individuals with germline pathogenic *TP53* variants potentially has multiple components some of which have MBS items numbers and some of which do not. Clinicians are typically hesitant to recommend risk management options if there is no associated Medicare rebate which also generally means limited accessibility or unavailability of the risk management option.

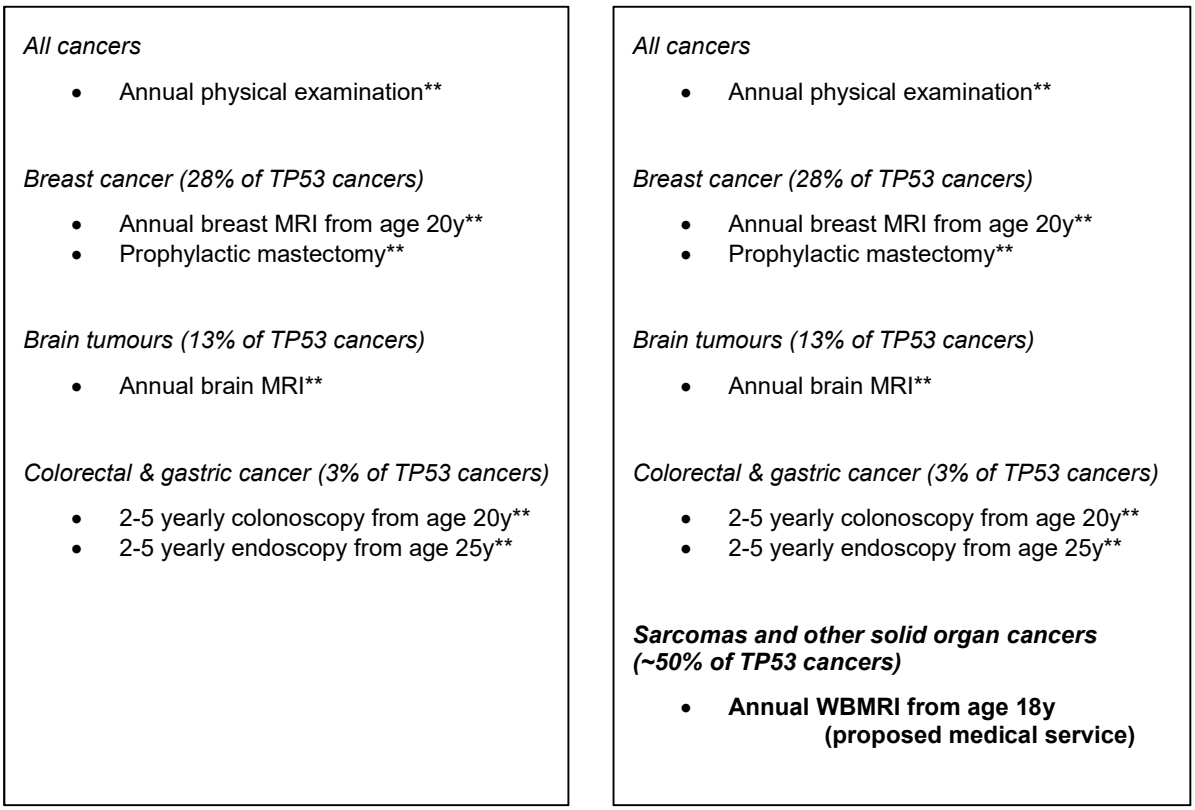
The current components of the eviQ risk management guidelines are:

1. Annual clinical review and physical examination**
2. Avoid environmental or behavioural risks (sun, smoking, unnecessary radiation exposure)
3. Offer prophylactic mastectomy for women under 50 years**
4. Annual breast MRI from age 20 years **
5. Offer risk reducing medication for breast cancer
6. Consider 2-5 yearly colonoscopy from age 20 years**
7. Consider 2-5 yearly endoscopy from age 25 years**
8. Consider annual brain MRI**
9. Consider **annual WBMRI (proposed medical service)**

**Associated with MBS item number

The appropriate comparator groups are the components of the eviQ risk management guidelines currently associated with Medicare item numbers compared to components of the eviQ risk management guidelines currently associated with Medicare item numbers with the addition of annual WBMRI (see figure below).

Figure: Comparator groups for proposed medical service



**Currently associated with an MBS item number

It is not intended that WBMRI replace any of the eviQ risk management options, because breast and brain MRI requires a dedicated sequence and protocol, WBMRI is not reliable for detection of gastrointestinal tumors, and clinical history and examination is required for surveillance of melanoma or other skin cancers.

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

1. Annual clinical review and physical examination: MBS item number 132
2. Breast MRI: MBS item number 63464
3. Prophylactic mastectomy and reconstruction: MBS item number 31524
4. Annual brain MRI: MBS item number 63001
5. 2-5 yearly colonoscopy from age 20 years: Medicare item number 32226
6. 2-5 yearly endoscopy from age 25 years: Medicare item number 30473

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):

Please see attachment 2.

The annual clinical review and physical examination will be performed by the family cancer/genetics clinician who will also request brain MRI, breast MRI (females only), colonoscopy and endoscopy for the patient. Breast and brain MRIs are performed and read by experienced radiologists. Similarly, colonoscopies and endoscopies are performed by experienced gastroenterologists. Clinical reports are returned to the family cancer/genetics clinician.

There are two potential outcomes:

1. No suspicious lesions identified. The patient repeats physical examination, breast and brain MRI, colonoscopy and endoscopy in following years

2. A suspicious lesion is identified and additional imaging and/or biopsy is required. In due course, if no malignancy is detected then the patient repeats physical examination, breast and brain MRI, colonoscopy and endoscopy in following years. If malignancy is detected, treatment in undertaken.

(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:

The proposed medical service (annual whole-body MRI) is to be added to the existing Medicare rebated management. See Q38.

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

Current eviQ risk management guidelines for *TP53* pathogenic variant carriers includes consideration of annual WBMRI. However, the cost of the scan and the lack of monetary rebate means that WBMRI is rarely considered and often not offered by radiology services. Many adult *TP53* variant carriers in Australia (~100 individuals) access annual WBMRI via the research program, the Surveillance study in Multi-Organ Cancer prone syndromes (ACTRN12613000987763). Introducing the proposed medical service would provide access to annual WBMRI to adult *TP53* variant carriers throughout Australia at an affordable cost.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

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

The addition of WBMRI to existing management will enable **detection of solid cancers (~50% of *TP53* cancers)** other than breast and brain cancers (that currently have funded risk management options). The estimated cancer rates for individuals with germline pathogenic *TP53* variants are amongst the highest known, with lifetime cancers risks of 90% for men and approaching 100% for women. The most common cancers observed in these populations are breast cancer (28%), sarcomas (23%), brain (13%), adrenocortical carcinomas (11%), and then a broad spectrum of other **solid malignancies (~30%)** including bowel, prostate and lung. In all of these cancers, surgical resection is essential to good outcomes. Consistent with a role for early detection, breast MRI has been shown to identify breast cancers at an earlier stage and smaller size. Early detection of sarcomas and other solid malignancies is key to successful resection and favorable outcomes.

In the largest international study conducted to date, a meta-analysis evaluating baseline WBMRI in 578 germline pathogenic *TP53* variant carriers (mean age 33 y) had a detection rate for new, localised primary cancers of 7%. Essentially 1 in 14 individuals undergoing baseline WBMRI had a new asymptomatic cancer detected which enabled treatment with curative intent.

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

☒ Superiority
☐ Non-inferiority

44. 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: No adverse events are associated with WBMRI, which is widely accessible in the community and has been available for over a decade.

Clinical Effectiveness Outcomes: The detection of surgically resectable cancers at a curable stage

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

There are approximately 160 adults with germline pathogenic *TP53* variants currently identified by Australian familial cancer clinics, excluding the Northern Territory, ACT and Tasmania. Allowing for increased referrals of eligible subjects, we anticipate a prevalent population of 200-250 adults would be eligible.

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

The service would be provided once each year.

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

From 18 years to age 65 years. Above 65 years of age, the background incidence of cancer and competing causes of mortality begin to rise, and it is arguable that WBMRI may not provide the same benefit as in younger populations.

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

100

49. 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:

Leakage will be minimal, with the appropriate controls on eligibility and limiting referrals to the centres and clinical groups described above. However, the true prevalence of carriers of *TP53* mutations may reach one in 20,000 of the population, which may mean that there may be up to 1,250 carriers in Australia.

PART 8 – COST INFORMATION

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

$1500 per whole body scan

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

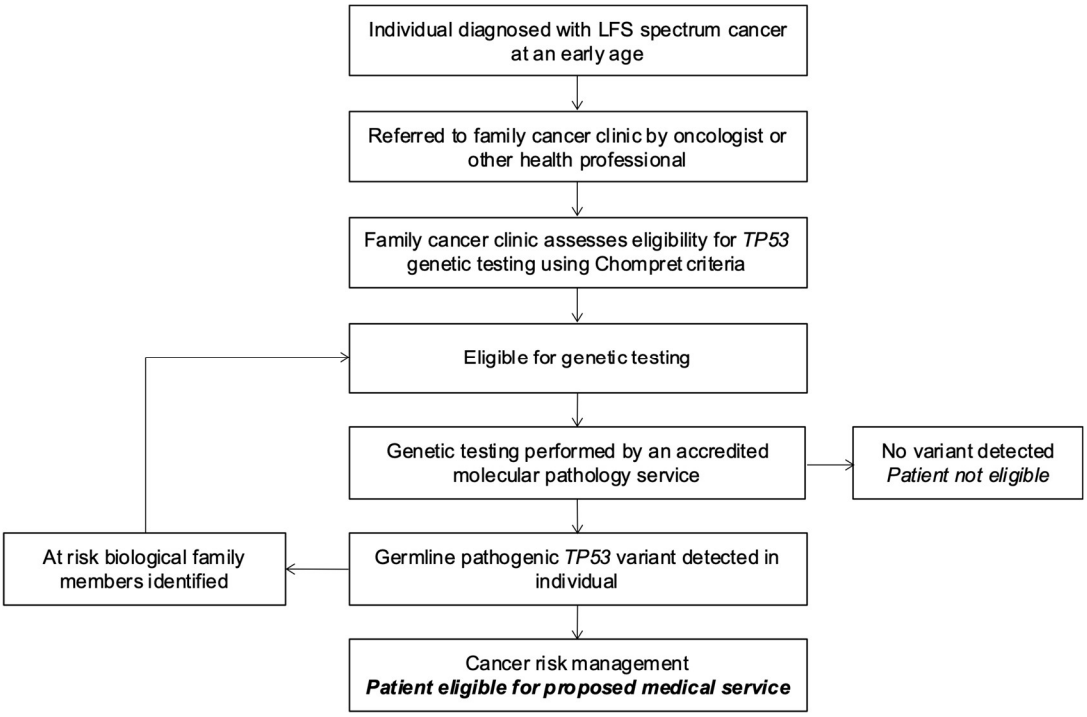
Approximately one hour, depending on instrument.

52. 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 5 – Diagnostic Imaging Services
Proposed item descriptor: MRI – whole body scan for the detection of cancer, the request for the scan identifies that the person is aged 18-65 years of age and has a high risk of developing solid cancer due to the presence of a pathogenic or likely pathogenic variant in the *TP53* gene. Fee: $1500

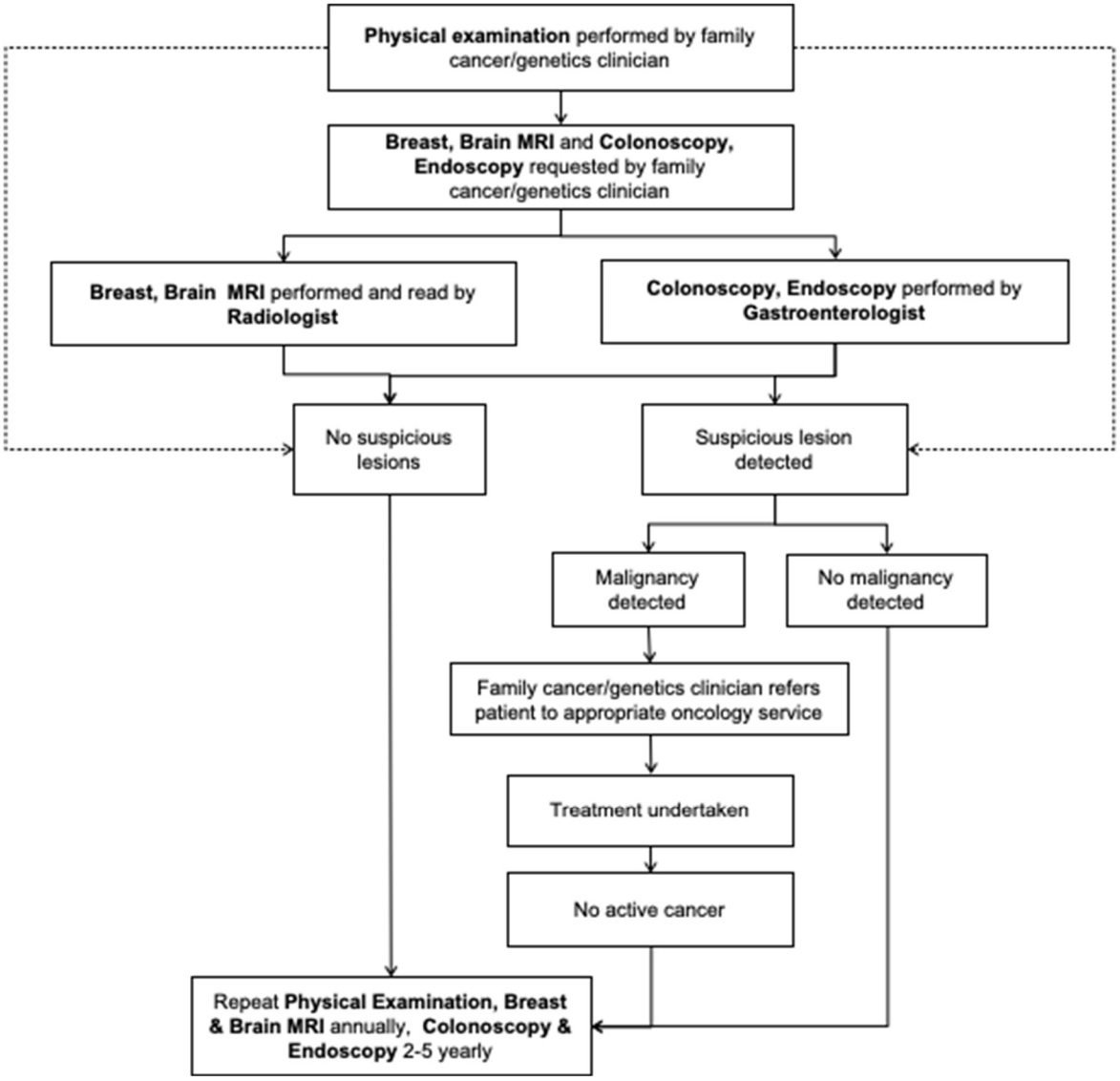
Attachment 1

Q26. Current clinical management pathway before patients would be eligible for the proposed medical service



Attachment 2.

Q40. Current clinical management pathway that the patients may follow from the point of receiving the comparator onwards.



REDACTED