



Australian Government

Department of Health

Ratified PICO Confirmation

Application 1668:

**Whole body magnetic resonance imaging
(WBMRI) for detection of cancer in individuals
with a germline pathogenic or likely pathogenic
Tumor Protein 53 (TP53) variant**

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC).

Table 1 PICO for whole body magnetic resonance imaging (WBMRI) for surveillance of patients with a pathogenic or likely pathogenic *Tumour Protein 53 (TP53)* variant: PICO Set 1

Component	Description
Population	Individuals aged 65 years or less who have tested positive for a pathogenic or likely pathogenic germline variant of the <i>Tumor Protein 53 (TP53)</i> gene.
Prior tests	Genetic testing to confirm germline pathogenic <i>TP53</i> variant status.
Intervention	Annual non-contrast whole body magnetic resonance imaging (WBMRI) surveillance for the early detection of cancer, in addition to other standard risk management options available in current practice (including but not limited to, physical examination, biochemical tests, brain and breast MRI, colonoscopy and endoscopy).
Comparator/s	Standard Medicare Benefits Schedule (MBS)-funded diagnostic options available in current practice (including but not limited to, physical examination, biochemical tests, brain and breast MRI, colonoscopy and endoscopy).
Reference standard	The reference standard for WBMRI is the histological diagnosis of the lesion identified (malignant, pre-malignant or benign).
Outcomes	<p>Safety including any potential risk of harm to patient.</p> <p>Number of cancers detected, number of cancers detected at curable stage.</p> <p>Overall survival, health-related quality of life (including psychosocial impact and value of knowing).</p> <p>Diagnostic accuracy (sensitivity, specificity, false positives, false negatives rate).</p> <p>Healthcare resources.</p> <p>Cost-effectiveness.</p> <p>Total Australian Government healthcare costs.</p>
Assessment questions	What is the safety, effectiveness and cost-effectiveness of annual surveillance WBMRI plus standard risk management options versus standard risk management alone in monitoring patients for early detection of cancer who have a pathogenic or likely pathogenic germline <i>TP53</i> variant?

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of whole body magnetic resonance imaging (WBMRI) for surveillance of patients with a germline pathogenic or likely pathogenic variant of the *Tumor Protein 53 (TP53)* gene for the early detection of cancer was received from the Australian Genomic Cancer Medicine Centre Ltd (Omico) by the Department of Health.

The application claimed that use of WBMRI in addition to standard risk management options results in superior health outcomes compared to standard risk management options alone.

PICO criteria

Population

The requested population are patients who have a pathogenic or likely pathogenic germline variant of the *TP53* gene, confirmed by an accredited molecular pathology laboratory.

TP53 and Li-Fraumeni syndrome (LFS)

Germline pathogenic variants in the *TP53* gene cause Li Fraumeni Syndrome (LFS). LFS is a rare condition (affecting between 1/5,000 and 1/20,000 of the population; Gonzalez 2008; Laloo 2003) and is associated with a high risk of developing cancers in multiple tissues.

The condition is named after Li and Fraumeni who described four families in which the high frequency of cancer suggested a familial syndrome of neoplastic diseases (Li and Fraumeni 1969). This was later expanded to 24 families in which bone and soft tissue sarcomas, breast cancers, brain tumours, leukemia and adrenocortical cancers (ACC) were seen in high incidence (Li and Fraumeni 1988). In 1990, LFS families were found to harbour germline *TP53* variants (Malkin 1990; Srivastava 1990). Petitjean (2007) identified over 700 *TP53* variants in the germline of approximately 760 families. LFS is inherited in an autosomal dominant manner with most individuals inheriting a *TP53* pathogenic variant (Schneider 1999); *de novo* variants are reported to constitute between 7% and 20% of cases (Renaux-Petel 2018).

PASC noted that TP53 is the only gene that has been definitively associated with LFS, but that not all people with a TP53 variant will have LFS.

The definition of LFS has evolved over time and the Chompret criteria were more recently proposed to aim to identify the most suitable candidates for *TP53* genetic testing (Chompret 2001; Bougeard 2008; Tinat 2009). The criteria take into account individuals with multiple malignancies (which may be due to *de novo* variants) with 21–35% of those meeting the updated criteria shown to be carriers of *TP53* variants (Bougeard 2008; Gonzalez 2009; Ruijs 2010). The Chompret criteria (Bougeard 2015) are as follows:

A proband with a tumour belonging to the LFS tumour spectrum (proband with tumor belonging to LFS tumor spectrum (e.g., premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma) 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 breast cancer diagnosed before the age 31 years.

PASC noted that the Chompret criteria do not identify all carriers of pathogenic or likely pathogenic TP53 variants. PASC also noted that broader selection criteria for genetic testing for TP53 variants, such as the

ERN GENTURIS criteria, might be used by jurisdictional genetics services to determine access to testing in public hospitals.

Frebourg (2020) considers that the diversity of clinical presentations associated with germline *TP53* alterations justifies the expansion of the LFS concept to a wider cancer predisposition syndrome designated heritable *TP53*-related cancer (h*TP53rc*) syndrome.

The application specified that WBMRI is proposed 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.

only for patients with a pathogenic or likely pathogenic germline variant of *TP53*, being considered clinically actionable variants as defined by the American College of Medical Genetics (ACMG; Richards 2015). The applicant further clarified that all individuals with germline pathogenic or likely pathogenic *TP53* variants be eligible for WBMRI whether they meet clinical criteria such as classic LFS, Chompret LFS, h*TP53rc* or not; it was for this reason that '*TP53* variant' carriers was used in the description of the eligible population rather than other less specific terms such as LFS. The applicant further stated that consistent with international guidelines (Frebourg 2020), individuals with germline pathogenic or likely pathogenic *TP53* variants (including those with h*TP53rc*) be eligible for surveillance including annual WBMRI. Patients with *TP53* variants of uncertain significance (VUS) are not included in this proposal for funding.

PASC noted that individuals with germline TP53 variants include but are not limited to patients with Li-Fraumeni syndrome (LFS), and agreed with the applicant that germline TP53 variants should be the eligibility criterion, and that the more comprehensive term, "heritable TP53-related cancer (hTP53rc) syndrome", is preferred.

Natural history of LFS

Germline pathogenic *TP53* variants are highly penetrant and carriers are characterised by an early age of onset of several different cancer types and an extremely high lifetime cancer risk. Individuals with LFS have an approximately 50% risk of developing cancer by age 40, and up to a 90% percent risk by age 60, while females have nearly a 100% risk of developing cancer in their lifetime due to their markedly increased risk of breast cancer. Many individuals with LFS develop two or more primary cancers over their lifetime (NORD 2021)¹. 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 (Petitjean 2007).

The application stated that 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 cancer types are observed also occurring at ages much younger than the general population.

The application stated there have been no formal studies evaluating life expectancy but with the early onset of cancers and poor survival it is estimated by Evans and Ingham (2013) to be on average below 40 years of age.

¹ Accessed June 28, 2021 <https://rarediseases.org/rare-diseases/li-fraumeni-syndrome/>

Prior testing

The application stated that the service would apply only to individuals who are carriers of pathogenic or likely pathogenic germline *TP53* variants (including both inherited and *de novo*), where the diagnosis was confirmed by an accredited molecular pathology laboratory.

Frebourg (2020) notes that whereas the interpretation of *TP53* variants that are predicted to result in loss of function, such as nonsense or frameshift deletions or insertions, is usually obvious, the interpretation of missense variants, representing the majority, is often challenging and requires specific expertise. The most common consequence of germline variants causing h*TP53*rc syndrome is the functional inactivation of the protein.

Classification of *TP53* missense variants, in agreement with the ACMG/AMP guidelines, is based on several considerations including phenotypical data; frequency of the variant in the general population, as reported by the Genome Aggregation Database; bioinformatic predictions of the variant's impact on protein or RNA splicing using different algorithms; and functional analyses of the variants performed using different *in vitro* assays performed either in yeast or cultured cells (Frebourg 2020). The applicant clarified that phenotypic data should not be restricted to those identified as fulfilling the Chompret criteria as (i) phenotypic data are not always collected in families meeting Chompret criteria and (ii) with the inclusion of *TP53* on many cancer sequencing panels, variant carriers are increasingly being identified with a broad range of phenotypic features.

Access to Prior testing

The applicant noted that currently, germline *TP53* testing is accessed via the MBS for individuals suspected of hereditary breast and ovarian cancer (HBOC), as one of four genes suspected to increase risk of these cancers (MBS items 73296, 73297).

PASC acknowledged the current limited availability of testing for TP53 variants (affected individual and cascade) on the MBS.

The applicant stated in further correspondence that LFS has been recognised and tested via various institutional and out-of-pocket mechanisms for more than 20 years; this may also include funding through hospitals and departmental funds. The applicant further clarified that genetic testing in Australia takes place in public hospitals and so is State/Territory-funded, with clinical criteria determining who has access to testing.

The applicant considered the current application analogous to the past MSAC [Application 1098](#) for reimbursement since 2008 of breast MRI for women with HBOC, who have only recently obtained an MBS item for reimbursed genetic testing. The applicant expressed confidence that existing funding mechanisms allowed for appropriate access to *TP53* testing and counselling. The applicant stated that MBS funded testing for *TP53* variants would not have an impact and that currently, there was equity in access to testing.

PASC noted that TP53 testing is currently funded by State/Territory genetics services; the current application does not propose to alter these funding arrangements. PASC also noted that rural/remote patients may incur additional accommodation and travel expenses if surveillance were to include additional testing by WBMRI.

In response to the answer provided in Question 25 of the application that "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”, consultation feedback stated:

“Across Australia, genetic services are delivered under a number of different models, and not all genetics services have familial cancer clinics or offer risk management-based clinical services. While I completely agree that the intervention should only be ordered by Specialists with experience in cancer genetics, and in consultation with a qualified clinical geneticist, the stipulation of a qualified clinical geneticist in a family cancer/genetics clinic as the ordering clinician may create a barrier to access for patients in several states”.

The applicant responded that the clinical risk associated with carriage of variants in *TP53* is arguably the greatest for any heritable cancer syndrome, and the spectrum of cancers observed mandates access to specialist oncology and diagnostic support services. It is arguable that in the first instance, the management of affected families should be established by experts in cancer genetics, in the context of appropriate multidisciplinary services. There would be secondary benefits in terms of gathering data to extend evidence for costs, clinical and social utility.

The applicant also noted, however, that there are mixed models of care for such individuals, which may involve initial assessment and diagnosis of families, with subsequent care (including WBMRI) being run in joint partnership with non-specialist services. The application considered that there is a tension between ease of access to services that are arguably standard of care, and careful establishment of novel and complex management in centres which can over time disseminate such models of care more broadly. The applicant stated that they had prioritised the latter, but would take advice from the Department.

Age of the eligible population

The application limited the population to patients between age 18 and 65.

After lodging the application, the applicant noted in further correspondence that the Zero Childhood Cancer Program is being extended to most Australian children with cancer, and may well identify many patients who carry *TP53* variants. An extension of the adult Surveillance study in Multi-Organ Cancer Prone Syndromes (SMOC+) programme in paediatrics has been developed to provide research-based access to screening. The application noted, however, issues such as the requirement for sedation, complications of consent, and the smaller amount of data available for children lead the applicant to make this current application solely for adults.

PASC considered the meta-analysis of TP53 variant carriers reported in Bougeard (2015), in which the age at first tumour onset was 18 years or less in 41% of the cohort, and noted that neither the eviQ risk management guidelines (Kratz 2017) nor the ERN GENTURIS (European Reference Network – Genetic Tumour Risk Syndrome) guidelines limited WBMRI to adult carriers. PASC advised that children should also be included in the proposed population.

The application noted that 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.

PASC accepted the applicant’s rationale for excluding those aged over 65 years in the proposed population.

Figure 1 presents the prior tests to identify those with pathogenic or likely pathogenic *TP53* variants who would then be eligible for the requested service.

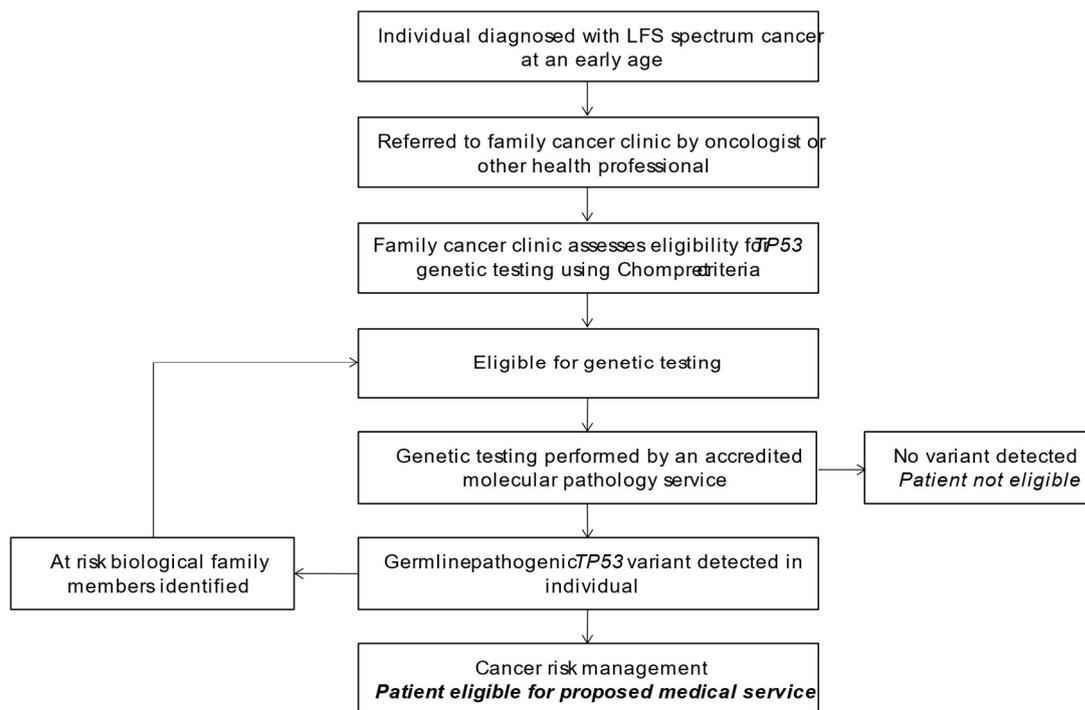


Figure 1 Current prior testing pathway before patients would be eligible for the proposed medical service

Source: Attachment 1, p29 of the application.

The application anticipated a prevalent population of 200-250 adults would be eligible for the service.

PASC noted the applicant's estimate of the true prevalence of carriers of TP53 variants may reach one in 20,000 of the population and that there may be up to 1,250 carriers in Australia.

Intervention

The proposed medical service is annual WBMRI for individuals with germline pathogenic *TP53* variants, which is not restricted to those with LFS. The applicant clarified that “[a] family is classified as having LFS if they meet classic LFS criteria. Approximately 70% of families meeting LFS criteria carry a pathogenic or likely pathogenic *TP53* variant. In essence an individual may carry a *TP53* variant but not have LFS and conversely, may have LFS but not carry a *TP53* variant.”. The intervention is proposed to be used in addition to the several diagnostic procedures that constitute standard risk management for patients with a germline pathogenic or likely pathogenic variant of *TP53*.

The applicant provided a further description of the intervention:

Whole body MRI is a screening tool that scans from vertex to feet using conventional MR imaging sequences acquired in the axial or coronal plane. Section thickness for each sequence is approximately 8mm with 2mm gap. Pixel size is not more than 2 x 2 mm in-plane for any sequence. The non-contrast scan takes approximately one hour and is designed to detect lesions of approximately 10mm in size or greater.

PASC noted there was no universally accepted definition for WBMRI. One recommendation for a set of acquisition sequences for oncologic WBMRI is provided in Morone (2017), see Table 2.

Table 2: Recommended acquisition sequences for WBMRI

Sequence	Standard Protocol	Optional Consideration	Acquisition Mode
T1-weighted whole body	3D gradient-echo (including Dixon technique), 2D gradient-echo or 3D fast spin-echo T1-weighted Axial imaging preferred with maximum section thickness of 5-7mm	Supplemental coronal or axial T1-weighted imaging	Breath-hold
T2-weighted whole body		Turbo spin-echo HASTE with or without fat suppression with maximum 5- to7-mm section thickness matched to T1-weighted imaging	Free breathing (respiratory triggered)
Whole body DWI	Axial projection with STIR fat suppression, 5- to7-mm section thickness matched to T1- and T2-weighted imaging 2 b values (50-100 s/mm ² , 600-1000 s/mm ²) Highest b value multiplanar reformats and 3D maximum-intensity-projection reconstructions		Free breathing
Whole-spine sagittal T1-weighted		T1-weighted turbo spin-echo 4- to 5-mm section thickness for evaluating bone disease	Free breathing
Whole-spine sagittal T2-weighted or STIR		T2-weighted with or without fat suppression 4- to 5-mm section thickness for evaluating bone disease	Free breathing

Source: Morone 2017

DWI = diffusion-weighted imaging; HASTE = half-Fourier-acquired single-shot turbo spin echo; mm² = square millimetre; STIR = short-tau inversion recovery

PASC requested that advice be sought from the Royal Australian and New Zealand College of Radiologists (RANZCR) to define a minimum set of sequences to define an adequate oncologic WBMRI examination.

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.

The application stated that according to clinical practice guidelines nationally and internationally, optimal clinical management of individuals with germline pathogenic *TP53* variants now requires consideration of annual WBMRI.

The eviQ cancer risk management guidelines (Kratz 2017) for adults with germline *TP53* variants 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.

Other international guidelines (Daly 2021) also recommend annual WBMRI.

All of the investigative services recommended by eviQ, other than annual WBMRI, are associated with current MBS items.

Standard risk management for patients with *TP53* variants is complex, evolving, and patient-specific. Additionally, there are similar, but not identical, surveillance protocols available. For example, the ERN GENTURIS surveillance guidelines (Freboung 2020) only recommend colonoscopy in adults who have received abdominal radiotherapy for the treatment of a previous cancer or if there is a familial history of colorectal tumours suggestive of an increased genetic risk.

WBMRI is proposed to be conducted in addition to the other nominated investigative services and is not anticipated to replace any. The application states that the addition of WBMRI to existing management will enable detection of solid cancers (~50% of *TP53* cancers) other than breast and brain cancers.

PASC discussed the consequences of false positive results resulting from non-specific findings from WBMRI. PASC questioned whether RANZCR accreditation for MRI included sufficient experience in WBMRI to reduce the likelihood of false positive results.

Comparator

Current cancer risk management in individuals with germline pathogenic *TP53* variants potentially has multiple components, some of which have MBS items 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 application proposed that the appropriate comparator is the components of the eviQ risk management guidelines that are currently associated with Medicare item numbers. This would include annual physical examination, annual breast MRI from age 20 for women, prophylactic mastectomy, annual brain MRI as well as 2-5 yearly colonoscopy from age 20 and 2-5 yearly endoscopy from age 25.

As previously stated, standard risk management is complex, evolving and patient-specific.

The application stated 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 tumours, and clinical history and examination is required for surveillance of melanoma or other skin cancers. The applicant further clarified that “[d]edicated breast MRI is a diagnostic imaging protocol that commonly scans with section thicknesses no greater than 2.5mm and in-plane pixel size of 1 x 1 mm or lower [this differs to the WBMRI protocol described above]. This ensures fine detail imaging and allows detection of small tumours (<5mm). The situation is similar with dedicated brain MRI”. The applicant re-iterated that “[g]iven breast and brain cancers are common in *TP53* variant carriers, the applicant feels retention of individual brain and breast MRIs essential for earliest possible detection of malignancy in these organs.”

The applicant further confirmed that funding of WBMRI would not replace (partially or completely) any other investigative tests beyond those defined by eviQ risk management.

PASC accepted the nominated comparator, which was standard MBS-funded risk management options.

Reference standard

The reference standard for WBMRI is the histopathological diagnosis of cancer. The applicant expressed agreement with this proposed reference standard, if what was meant was that “identification of cancer by standard approaches, including clinical presentation and subsequent work up leading to a histopathologically confirmed diagnosis of cancer”.

PASC accepted the nominated reference standard.

Outcomes

The application (and further correspondence from the applicant) states that the scan will yield three potential outcomes:

A) No Suspicious lesions

On expert radiologic review, requires no further follow up. These include normal or anatomic variations, or obviously or known non-malignant lesions.

B) A lesion that requires additional imaging or more frequent surveillance

These include a dedicated scan in 3 months to determine stability or progression, or a test that provides additional information that may help the radiologist determine likely risk. The most commonly performed tests include targeted ultrasound, and targeted MRI with dedicated sequences or contrast. In the Australian cohort of 91 individuals, with a median follow up of 4 years, 63 follow up investigations were performed without need for biopsy. In order of frequency:

- Ultrasound (n=24);
- Computed tomography (CT) (n=20; most commonly chest CT);
- Dedicated MRI sequences (n=13);
- Positron emission tomography (PET) (n=3);
- Endoscopy (n=2); and
- Thallium scan (n=1).

C) Lesion(s) necessitating biopsy to confirm malignancy

In addition to these outcomes, an assessment should evaluate comparative outcomes such as:

- Overall survival;
- Cancers detected;
- *Cancers detected at a curable stage;*
- False positives, false negatives, estimates of diagnostic accuracy including sensitivity, specificity;
- Time to cancer diagnosis;
- Changes in clinical management (e.g., changes to frequency of additional imaging or surveillance, biopsy, treatment);
- Adverse events (of WBMRI, changes in clinical management and subsequent treatment);
- Health related quality of life outcomes (*PASC considered that health related quality of life outcomes should include psychosocial impact and value of knowing*);
- *Cost-effectiveness;*
- Health care resource use; and
- Financial impact.

The applicant stated that “[d]ata to assess overall survival is scant or non-existent”, noting that overall survival was not required for the breast MRI item approval for women at high risk for breast cancer. The applicant suggested that the primary endpoint should be number of cancers detected at a curable stage, to address lead time bias with the data sources available and because the proportion of primary/advanced stage cancers by histotype is reasonably known for most cancers.

PASC accepted the applicant’s request that “Cancers detected at a curable stage” be included as an outcome.

The applicant reiterated that the primary question is whether these cancers are likelier to be identified at an earlier and curable stage using WBMRI, compared to clinically ascertained cases in the absence of WBMRI.

The application did not make any claims regarding the value of knowing.

Assessment framework

Preliminary reviews of the literature provided by the applicant indicate a paucity of comparative outcomes in the evidence base. The Australia-specific data collected by the applicant as part of the Surveillance study in Multi-Organ Cancer prone syndromes (ACTRN12613000987763) are highly applicable and informative, but do not inform comparative effect versus the nominated comparator.

The recommendations for annual WBMRI in Kratz (2017) are largely based on Villani (2011;2016), non-randomised, cross-over studies comparing surveillance (consisting of WBMRI, brain MRI, breast MRI, mammography, abdominal and pelvic ultrasound) versus no surveillance. As such, the estimates of effect are not specific to WBMRI.

The application identified one randomised controlled trial (LIFSCREEN; Caron 2017; Caron 2018) of patients with *TP53* variants in France where patients were allocated to a standard surveillance arm “A” comprising a clinical exam, brain MRI, abdomino-pelvic ultrasound, complete blood count (CBC) for all patients, plus breast MRI and breast ultrasound for women aged over 20 years, or in “B” arm (A + WB diffusion MRI). Each patient repeated annually the process for at least 3 years. Only a subsequent study abstract (Caron 2018) published comparative results between the two treatment arms. The study did not demonstrate any statistical difference in overall survival between the two treatment arms, which may be due to insufficient follow-up.

Consequently, a linked evidence approach may be necessary, refer to Figure 2.

PASC accepted that a linked evidence approach would be required.

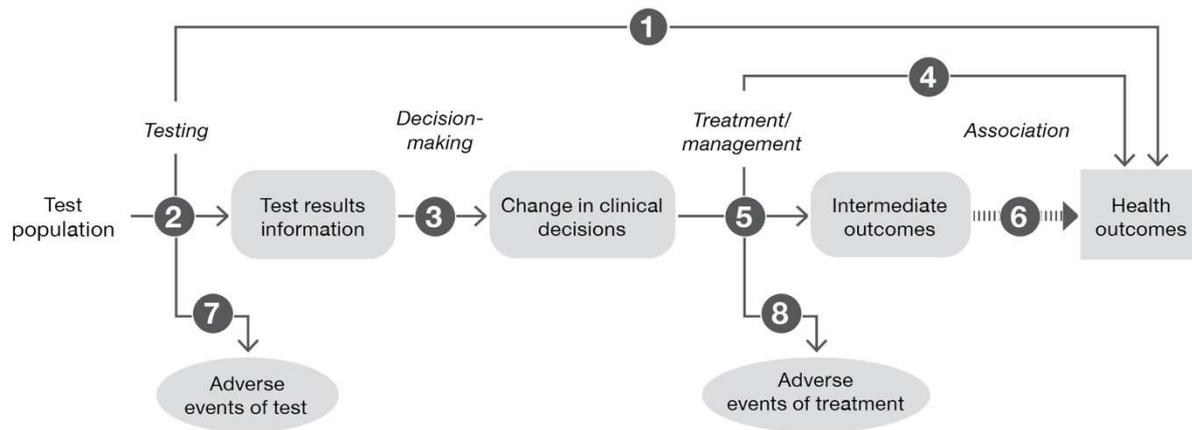


Figure 2 Generic assessment framework showing the links from the test population to health outcomes

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

Clinical management algorithms

The application provided a current clinical management algorithm in Attachment 2, p30.

Amended current and proposed algorithms developed for the PICO Confirmation are presented in

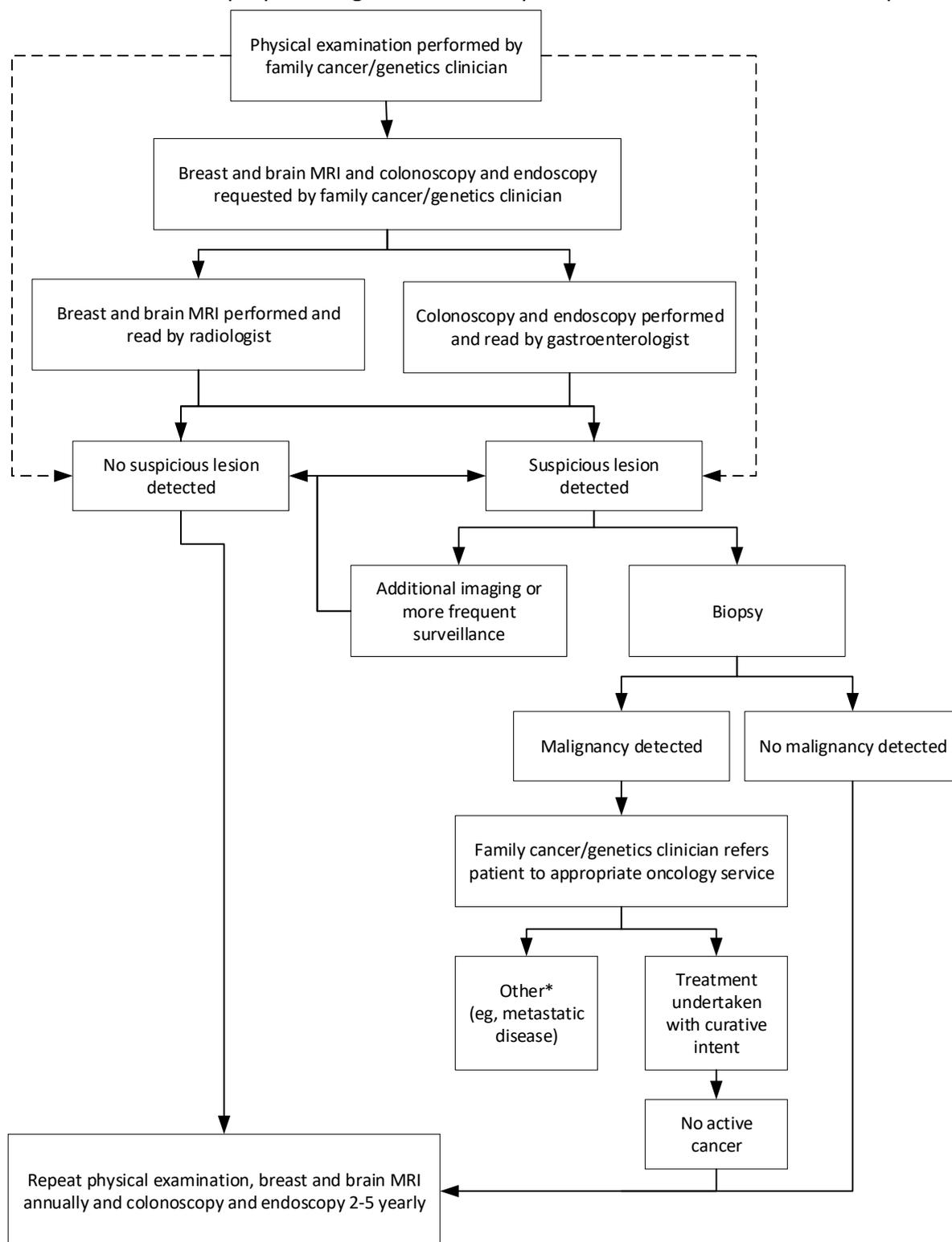


Figure 3 and

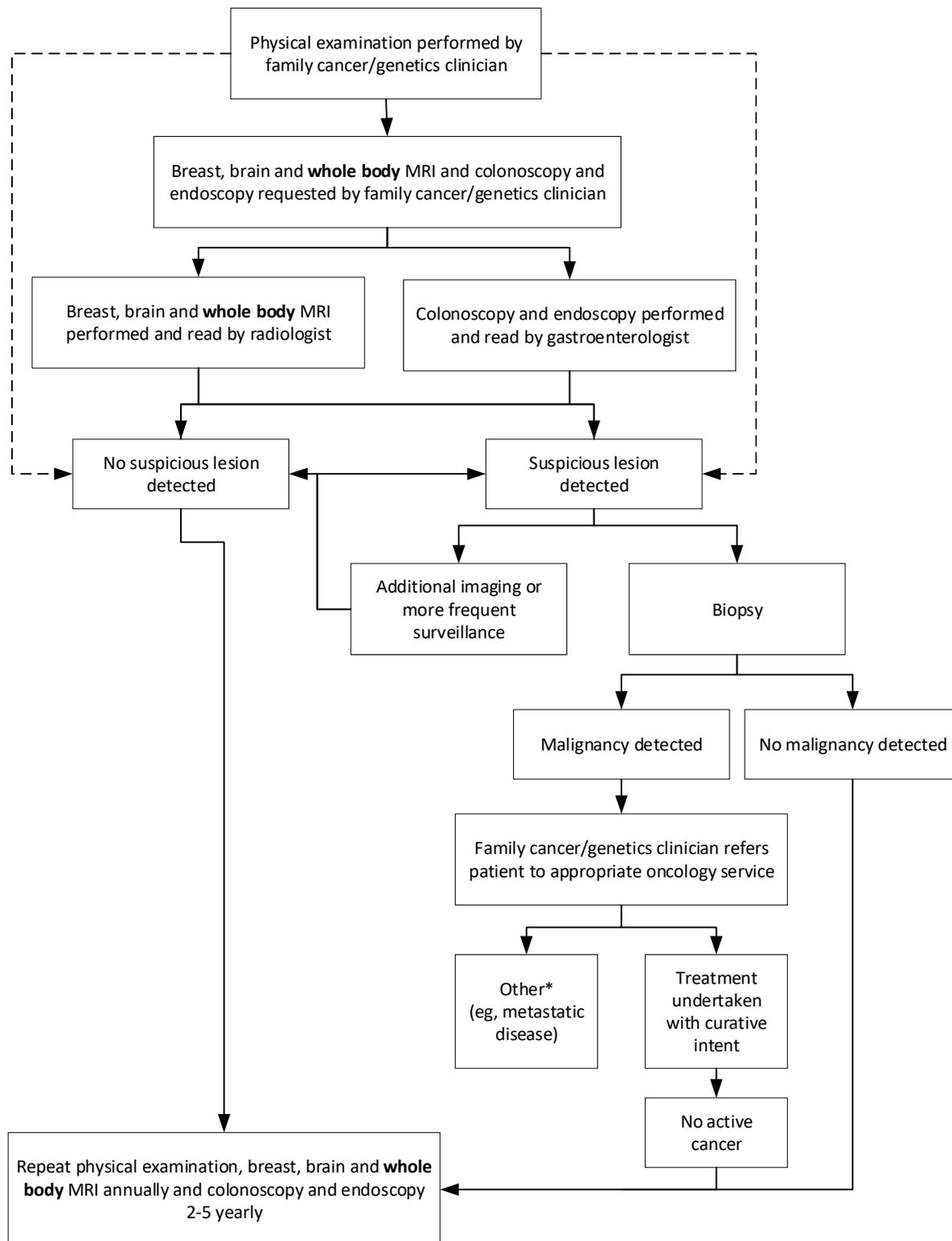


Figure 4, respectively. The applicant agreed with the amendments, but suggested that the treatment options downstream should be stratified into ‘treatment undertaken with curative intent’, and ‘other’, explaining that those treated and rendered disease-free may re-enter the program; while those with metastatic disease should be taken off the program, because of the frequency of imaging, the probability of metastatic disease being the issue, and because of the limited long-term benefit to flow from detecting a new primary.

PASC accepted the applicant's requested changes to the algorithms. These changes have been reflected in the algorithms below.

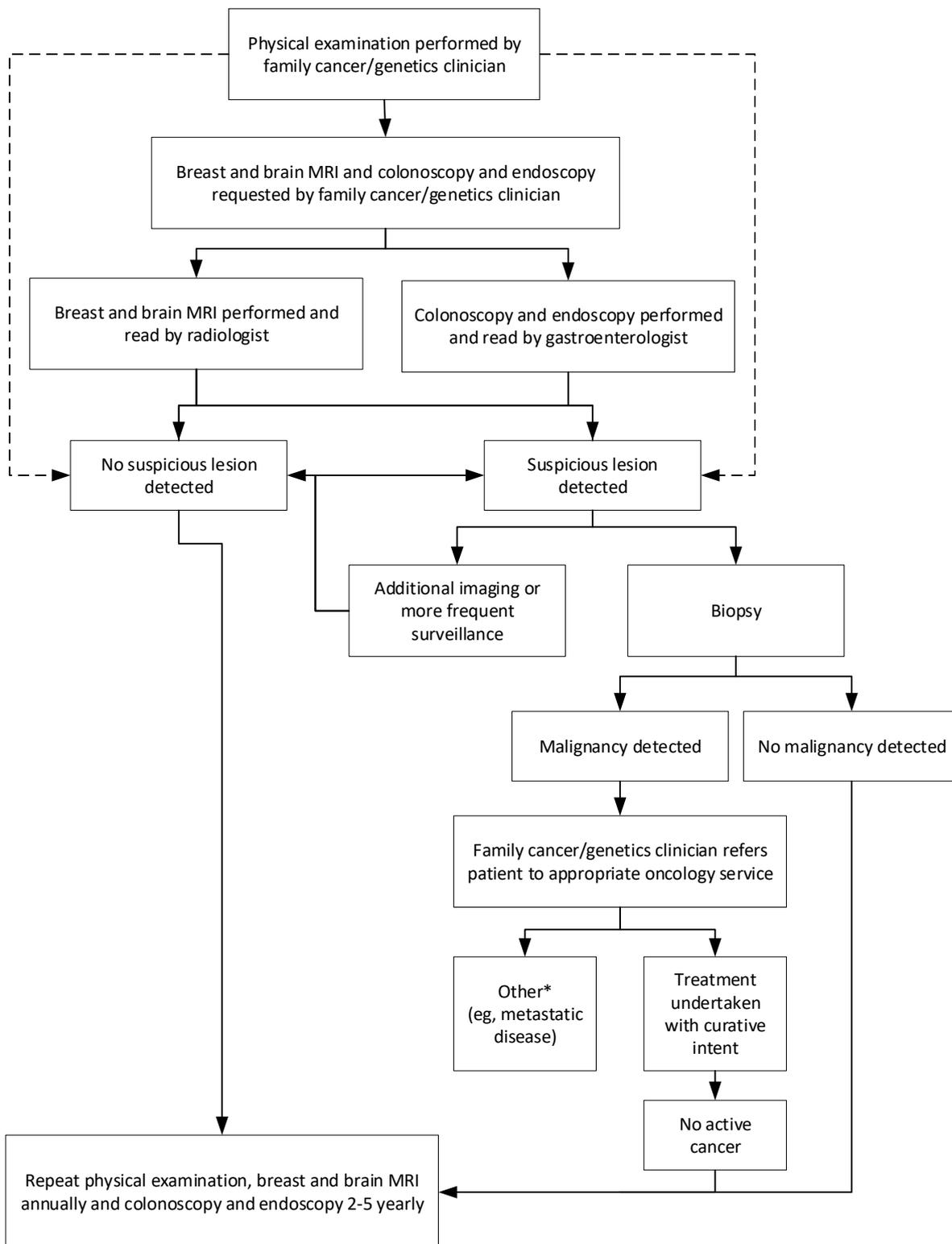


Figure 3 Current clinical management pathway for patients with a pathogenic or likely pathogenic *TP53* variant

* those with metastatic disease should be taken off the WBMRI program, because of the frequency of imaging, the probability of metastatic disease being the issue, and because of the limited long-term benefit to flow from detecting a new primary

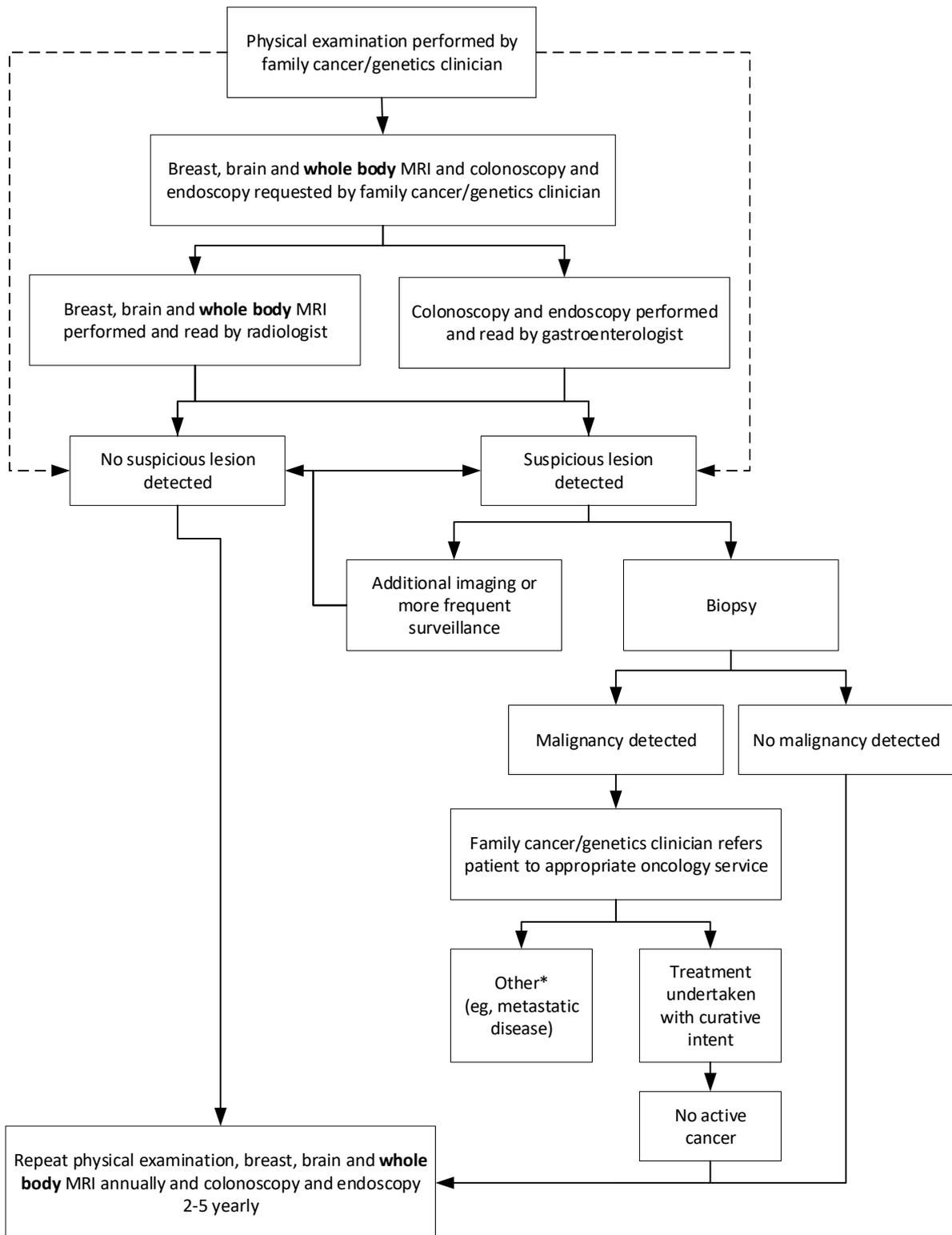


Figure 4 Proposed clinical management pathway for patients with a pathogenic or likely pathogenic *TP53* variant

* those with metastatic disease should be taken off the WBMRI program, because of the frequency of imaging, the probability of metastatic disease being the issue, and because of the limited long-term benefit to flow from detecting a new primary

Proposed economic evaluation

Considering that the clinical claim is that WBMRI in addition to standard of care is superior to standard of care alone in the early detection of cancer, a cost effectiveness or cost-utility analysis would be appropriate. Preliminary literature searches and discussions with the applicant who runs Australia-specific studies on WBMRI in *TP53* patients, indicate that there is sufficient evidence on which to examine the claim for adults.

PASC acknowledged the potential differences in costs (e.g., longer patient preparation for WBMRI in infants and young children, including possible sedation or anaesthesia with anaesthetist attendance) and clinical benefit between paediatric and adult populations, and the limitations of available evidence in the paediatric population.

*PASC therefore suggested that separate economic evaluations of WBMRI for children and adults with pathogenic *TP53* variants should be considered.*

Table 3 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Noninferior ^b	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior ^b	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

^a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

^b An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

The applicant proposed public funding for WBMRI for patients with a clinically actionable germline pathogenic or likely pathogenic *TP53* variant. The requested item descriptor provided in the application is presented below.

Category 5 – Diagnostic Imaging Services
MBS item *XXXX Whole body magnetic resonance imaging 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 <i>TP53</i> gene.
Fee: \$1,500.00

Amendments to the item descriptor are provided below.

PASC suggested further changes to the amended item descriptor (noted by struck-through and underlined text).

The applicant has indicated agreement with these changes. Consideration should be given to whether there should be separate item descriptors for those aged <18 and those aged 18-65 years.

Category 5 – Diagnostic Imaging Services
MBS item *XXXX MRI – whole body scan for the <u>early</u> detection of cancer, requested by a specialist or consultant physician in consultation with a clinical geneticist in a familial cancer or genetic clinic and the request identifies that: - the person is aged 18-65 years of age or less; and - has a high risk of developing solid cancer <u>malignancy</u> due to the presence of a <u>germline</u> pathogenic or likely pathogenic variant in the <i>TP53</i> gene. Restricted to one scan per 12 months.
Fee: \$1,500.00

The requested fee of \$1,500 compares with MBS fees (as at 5 July 2021) for MRI scans of the head ranging from \$336.00 to \$403.20 and MRI scans of both breasts of \$690.00. The application did not provide a justification for the requested fee.

PASC noted that justification of the proposed fee remained unresolved and should be addressed in the assessment report.

There are no associated applications related to the proposed health technology that are in progress.

Summary of public consultation input

Input was received from the following five (5) organisations:

- Australian Diagnostic Imaging Association (ADIA)
- Medical Oncology Group of Australia (MOGA)
- Royal College of Pathologists of Australasia (RCPA) - Australian Clinical Labs
- Genetic Alliance Australia
- The Royal Australian and New Zealand College of Radiologists (RANZCR).

Feedback was supportive of the application for public funding of whole-body MRI (WBMRI) for the detection of cancer in individuals with germline pathogenic *TP53* variants. One group noted that individuals with Li-Fraumeni syndrome have an extremely high lifetime risk of cancer.

Consultation feedback suggested the advantages were:

- WBMRI is a safe and sensitive method of screening for the proposed population.
- Early detection and management of inherited cancers which may result in downstaging of disease.
- Screening using WBMRI could provide a psychosocial benefit to patients and their families.
- Early detection may increase effectiveness of treatment.
- WBMRI is endorsed for the proposed use within international guidelines.
- Early detection of inherited cancers may limit the cancer burden on affected individuals and their families.

Disadvantages of the proposed testing were:

- Long examination times.
- Cost associated with attending additional appointments including loss of income, particularly for those in rural or remote communities.
- Potential psychological impact.
- The potential for false positives.
- Individuals with implants or devices that are contraindicated/unsafe in a magnetic field will be excluded from the service.

PASC noted that all of the consultation feedback was supportive of the proposal.

Further comments received in consultation feedback were:

- MSAC could consider the inclusion of other syndromes with increased risk of cancer such as Lynch Syndrome or those with *BRCA1* and *BRCA2* variants. The applicant agreed and stated that they see this as the future noting that *RB1*, *BRCA2*, *PTEN*, *VHL* and several other penetrant cancer syndromes have a broad spectrum of cancer susceptibility that may also be amenable to WBMRI. However, the applicant noted that specific data for the benefit of WBMRI for patients with variants in other genes remain to be generated.

Next steps

The applicant has indicated that the assessment should be conducted as a DCAR, with the applicant providing relevant data to inform the assessment.

Applicant comments on PICO Confirmation

Nil Comments

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