![Australian Government — Medical Services Advisory Committee]

Public Summary Document

Application No. 1668 – Whole-body magnetic resonance imaging for detection of cancer in individuals with germline pathogenic TP53 variants

Applicant: **Australian Genomic Cancer Medicine Centre Ltd (Omico)**

Date of MSAC consideration: **28-29 July 2022**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

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

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for whole-body magnetic resonance imagining (WBMRI) for the detection of cancer in individuals with germline pathogenic *TP53* variants who are at very high lifetime risk of developing new cancers. MSAC noted limitations in the clinical evidence, but considered WBMRI (without contrast agent) is safe and likely to be clinically effective, resulting in earlier detection and management of malignant lesions for this well-defined population with a high clinical need. MSAC also noted that WBMRI is recommended in national and international guidelines for this patient population. MSAC considered that the overall cost to the MBS would be small.

MSAC supported the following item.

Category 5 – Diagnostic Imaging Services
MBS item XXXX MRI – whole-body scan for the early 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 has a high risk of developing cancer malignancy due to heritable *TP53*-related cancer (h*TP53*rc) syndrome Restricted to one scan per 12 months
Fee: $1,500.00

Consumer summary

This is an application from the Australian Genomic Cancer Medicine Centre Ltd (Omico) requesting Medicare Benefits Schedule (MBS) listing of whole-body magnetic resonance imaging (MRI) for detecting cancer in individuals with a germline variant (also called a pathogenic or likely pathogenic germline variant) in the tumour protein 53 (*TP53*) gene.

Genes are made up of DNA and make proteins that determine many of our characteristics, such as what we look like and how our body functions. Human cells are made up of thousands of genes. But sometimes genes have mistakes in their coding, known as variants. Gene variants were previously called mutations in the medical literature.

In humans, the *TP53* gene is classified as a tumour suppressor gene, which means that it normally keeps cells from growing too fast or in an uncontrolled way. But, if the *TP53* gene has a variant in it, this means that the gene may not be able to control the growth of cells in the body. This uncontrolled cell growth can lead to cancer. A *TP53* variant can happen in a number of ways, but this application is for germline variants, which means they are heritable.

Magnetic resonance imaging (MRI) is a painless, non-invasive test and is performed inside a machine called the MRI scanner. Whole-body MRI just means that the MRI is used to scan the whole body, and then a computer generates a picture of the internal organs. A doctor can then see the location of any tumours and determine whether they are cancerous.

MSAC noted that the size of the population of people with a germline *TP53* variant is small but that they have a high risk of developing cancers over their lifetimes. Because of this small population, there is little research and therefore little evidence on how effective whole-body MRI is in monitoring this population for cancers. Nonetheless, MSAC noted that based on the limited evidence available, whole-body MRI is safe and effective in allowing more people with the *TP53* gene variant to detect their cancer earlier, which means that their cancer treatment can be started earlier. Because the number of people who would be eligible for this test is small, the cost would be relatively modest. Therefore MSAC, supported the listing of this procedure on the MBS.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported the listing of whole-body MRI for detection of cancer in individuals with a germline pathogenic or likely pathogenic germline variant of the *TP53* gene.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this is an application from the Australian Genomic Cancer Medicine Centre Ltd (Omico) requesting Medicare Benefits Schedule (MBS) listing of whole-body magnetic resonance imaging (WBMRI) for detection of cancer in individuals with a pathogenic or likely pathogenic germline variant of the *tumour protein 53* (*TP53*) gene (including individuals with Li-Fraumeni syndrome). MSAC noted that the surveillance is intended to be limited to once a year and to augment current surveillance (which includes some use of dedicated MRI breast and MRI brain) in the defined population. MSAC noted that WBMRI is currently inadequate for breast surveillance, or brain surveillance in the defined population, although in some imaging protocols, WBMRI has been successfully combined with formal diagnostic contrast enhanced brain MRI. MSAC noted that WBMRI is not a single well-defined entity (unlike e.g., "CT with contrast" or "FDG PET") but consists of a suite of multiple different sequences which vary from site to site and between indications with ongoing development of improved sequences.

MSAC noted that the WBMRI must be requested by a specialist or consultant physician in consultation with a clinical geneticist. MSAC considered that the advice from RANZCR that the WBMRI results can be reported by any radiologist who is accredited to report these MRI results appears reasonable.

MSAC noted that the proposed population comprises individuals who have been proven to have a germline pathogenic or likely pathogenic variant of *TP53* (heritable *TP53*-related cancer [h*TP53*rc] syndrome). MSAC noted that the initial application was limited to individuals aged 18 and older but, on the recommendation of PASC, this was expanded to include children. While the prevalence of individuals with *TP53* variants in Australia is unknown, MSAC noted that, internationally, prevalence is between 1/5,000 and 1/20,000 of the general population. Therefore, it is estimated that there would be approximately 330 eligible patients currently in Australia, with an increase of 10–15 new cases per year.

MSAC noted the high clinical need for cancer surveillance in the defined population, as men and women with h*TP53*rc syndrome have a 90% and 100% chance, respectively, of developing cancer in their lifetime; the highest risk of all cancer predisposition syndromes. MSAC noted the applicant's claim that annual surveillance with WBMRI will result in earlier detection of malignant lesions with the aim of improved survival due to earlier treatment.

MSAC noted the observation in the applicant's pre-MSAC response that MBS items for germline *TP53* testing were currently accessible for individuals suspected of hereditary breast and ovarian cancer through items 73296 and 73297 but that there are no equivalent items for these individuals with a sarcoma diagnosis. MSAC noted that there was some funding by State/Territory genetics services for *TP53* testing for other indications.

MSAC noted that following discussions between the Department and the applicant it was agreed that the eligible population did not need further limiting in the item descriptor, leaving access to the annual WBMRI as a clinical decision between the patient and their clinician. MSAC noted the advice of the Department that guidance on the germline pathogenic *TP53* variants could be provided in an explanatory note.

MSAC noted that all consultation feedback received was supportive of the application. MSAC noted that some consultation feedback suggested that the application could include some other populations with other heritable cancer risk syndromes that result in multi-organ cancer risk. However MSAC noted the applicant's pre-MSAC response advising that the evidence for other populations is even more limited than it is for h*TP53*rc syndrome. MSAC noted that, given the rapid evolution in gene technology with earlier identification of rare genetic conditions, the

Department expects to receive more applications to MSAC for similar small patient populations with other heritable cancer syndromes that confer a high lifetime risk for cancer, with clinical need for diagnostic services but may not necessarily have the strength of research data to support these services.

MSAC noted that MRI has been previously recognised as safe and effective and is acceptable for the defined population who are at an increased risk of developing post-radiation malignancy (e.g. as with computed tomography). MSAC considered the concern raised by ESC that the possible routine use of gadolinium as a contrast agent with WBMRI may lead to long-term gadolinium deposition in the brain[1] [2] and possible adverse effects in patients with acute kidney injury[3]. However, MSAC noted that contrast is not typically used for WBMRI for surveillance purposes.

MSAC considered the implications of false positives, such as anxiety and depression from screening, and possible associated costs. However, it was noted that because these patients are at such a high risk of cancer, the psychological impact of a false positive diagnosis appears to be different compared to people who have a level of risk aligned with the general population. For example, MSAC noted that the pre-MSAC response stated that there is evidence cited from the SMOC+ study that there is no observed impact on the Anxiety and Depression Score in individuals undergoing annual WBMRI over four years.

MSAC noted that the key studies on the effectiveness of WBMRI in detecting cancers in the defined population were the Caron (2017) LIFSCREEN randomised controlled trial (RCT) [4]; the Villani (2011) [5] and Villani (2016) [6] observational comparative study with 11 years follow up; the Surveillance study in Multi-Organ Cancers (SMOC) reported by SMOC+[7], Paixao (2018) [8] and O'Neil (2018) [9], and the Ballinger (2017)[10] meta-analysis.

MSAC noted ESC's observations that the only prospective RCT, LIFSCREEN, had flawed data which have only been presented at a conference, and which have not undergone peer review for publication. MSAC also noted that the study was considered to have a high risk of bias (due to neither patients nor investigators being blinded to surveillance allocation; not all relevant

[1] Petralia G, et al. (2021). 'Whole-body magnetic resonance imaging (WB-MRI) for cancer screening: recommendations for use', *La Radiologia Medica*, **126**(11):1434-1450

[2] Guo BJ, et al (2018). 'Gadolinium Deposition in Brain: Current Scientific Evidence and Future Perspectives', *Front Mol Neurosci.***11**:335.

[3] Schieda N, et al. (2018). 'Gadolinium-Based Contrast Agents in Kidney Disease: Comprehensive Review and Clinical Practice Guideline Issued by the Canadian Association of Radiologists', *Can Assoc Radiol J*. **69**(2):136-150

[4] Caron O, et al. (2017). 'Lung Adenocarcinoma as Part of the Li-Fraumeni Syndrome Spectrum: Preliminary Data of the LIFSCREEN Randomized Clinical Trial', *JAMA Oncology*, **3**(12):1736-1737

[5] Villani A, et al. (2011). 'Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study', *The Lancet Oncology*, **12**(6):559-567

[6] Villani A, et al. (2016). 'Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study', *The Lancet Oncology*, **17**(9):1295-1305

[7] Thomas D and Ballinger M. (unpublished). 'Unpublished data from the Australian SMOC+ whole-body MRI surveillance study in TP53 germline variant carriers'. Provided March 2022.

[8] Paixão D, et al. (2018). 'Whole-body magnetic resonance imaging of Li-Fraumeni syndrome patients: observations from a two rounds screening of Brazilian patients', *Cancer Imaging: the official publication of the International Cancer Imaging Society*, **18**(1):27.

[9] O'Neill AF, et al. (2018). 'Screening with whole-body magnetic resonance imaging in pediatric subjects with Li–Fraumeni syndrome: A single institution pilot study', *Pediatric Blood and Cancer*, **65**(2).

[10] Ballinger ML, et al. (2017). 'Baseline Surveillance in Li-Fraumeni Syndrome Using Whole-Body Magnetic Resonance Imaging: A Meta-analysis', *JAMA Oncology*, **3**(12):1634-1639.

outcomes being reported; and the relatively small sample size and short follow-up) and was likely to be underpowered to detect a difference in mortality.

In summarising the evidence base, MSAC noted that the clinical trial data were limited and were relatively low quality. MSAC noted that the overall findings of this limited evidence base were that:

- many patients in this cohort will comply with complex time-consuming surveillance protocols, including WBMRI
- WBMRI will likely detect additional malignancies (earlier) in this cohort but cannot replace dedicated brain MRI or dedicated breast MRI
- including WBMRI as part of surveillance improves patient "satisfaction" (i.e., there is a beneficial psychological impact due to the value of knowing).

However MSAC noted that due to the rarity of this condition there is, and likely always will be, a limited evidence base to support WBMRI screening recommendations for the defined population. MSAC noted that despite these limitations in the evidence, the addition of WBMRI to other surveillance techniques for Li-Fraumeni syndrome (LFS) has been recommended in domestic and international management guidelines[11][12][13][14], including the eviQ risk management guidelines (Australia)[15] and the NCCN guidelines (USA)[16]. MSAC concluded that WBMRI has equivalent or superior diagnostic accuracy compared to the current Australian surveillance protocol for patients with *TP53*-related cancers.

MSAC noted that for the economic evaluation, due to the acknowledged paucity of data, ESC agreed that a cost per life years gained approach was not viable and agreed with the DCAR's approach of adopting a cost-effectiveness analysis based on diagnostic accuracy outcomes. A one-year time horizon was used with the incremental cost-effectiveness ratio (ICER) expressed as the incremental cost per (i) positive new primary cancers (NPCs) correctly identified, and (ii) negative NPCs correctly ruled out.

MSAC noted that the DCAR reported the results of the cost-effectiveness analysis based on two data series - the first relied on data as reported by LIFSCREEN, while the second re-interpreted the LIFSCREEN data to reflect current surveillance protocols in Australia. This second approach used data only from the patients from the current Australian protocol plus WBMRI arm of the LIFSCREEN trial and estimated cost-effectiveness results assuming this population had been subjected to both treatment arms (the current Australian protocol and the current Australian protocol plus WBMRI). MSAC agreed with ESC that results from the second series, although not ideal, were more applicable and informative for the Australian context.

[11] Hanson H, et al. (2021). 'UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variants', Journal of Medical Genetics, 58(2):135-139.

[12] Frebourg T, et al. (2020). 'Guidelines for the Li–Fraumeni and heritable TP53-related cancer syndromes', European Journal of Human Genetics, 28(10):1379-1386.

[13] Consul N, et al. (2021). 'Li-Fraumeni Syndrome and Whole-Body MRI Screening: Screening Guidelines, Imaging Features, and Impact on Patient Management', AJR Am J Roentgenol. 216(1):252-263.

[14] Ballinger ML, et al. (2015). 'Surveillance recommendations for patients with germline TP53 mutations', Curr Opin Oncol. 27(4):332-7.

[15] eviQ Guidelines, available at https://www.eviq.org.au/cancer-genetics

[16] NCCN Guidelines Version 2.2022, Li-Fraumeni Syndrome Management.

MSAC noted that the estimated ICERs for a surveillance program including WBMRI (based on the second data series) were $23,494 per NPC correctly identified and $33,007 per NPC correctly ruled out.

MSAC noted that no sensitivity analyses were conducted around the costs of WBMRI which comprised the cost of one WBMRI and costs associated with false positives based on accuracy data from a three-year period. Sensitivity analyses were only conducted around the baseline value of prevalence of cancer in the defined population. MSAC noted that the analyses showed that the results were sensitive to variations in the prevalence of cancer. In particular, MSAC noted that a minimum cancer prevalence of 3.57% resulted in an ICER per positive NPC correctly identified of $38,079 and an ICER per negative NPC correctly ruled out of $55,758; and a maximum cancer prevalence of 13.21% resulted in an ICER per positive NPC correctly identified of $12,293 and an ICER per negative NPC correctly ruled out of $15,547.

MSAC considered that, given the low availability of high-quality data due to the small patient population with this rare disease, an accurate estimate of cost effectiveness is not possible, and greater weight could be placed on consideration of the international and domestic guidelines for management of individuals with germline pathogenic *TP53* variants and the relatively small and highly targeted financial impacts of the application.

MSAC noted that the net budget impact to the MBS was relatively low, at approximately $1 million per year, based on an LFS prevalence of 1 in 20,000 and approximately $3 million per year if the assumption of highest reported prevalence (1 in 5000) is applied.

MSAC noted that the fee is appropriate because WBMRI is time-consuming, particularly for people with *TP53* variants, where there is a high chance of a cancer being detected requiring a systematic search through all sequences. For instance, MSAC noted advice from RANZCR that studies can take anywhere from 45-90 minutes depending on patient size and scanner equipment, with 60-70 minutes a reasonable average time per scan. MSAC noted the applicant's pre-MSAC response did not agree that the fee should be lower for children even though children are smaller because the scan is more complicated for children (e.g. children under the age of eight may need anaesthesia) and may be more time consuming for them (e.g. they may need to exit and re-enter the scanner frequently, increasing the total length of time required to complete the scan).

MSAC noted that general concerns regarding the potential for overtesting and overtreatment in this population are not relevant, as the population is highly predisposed to developing cancer over the lifetime. MSAC considered that surveillance that finds no tumours or a benign tumour is still important clinical information, as well as for monitoring the potential future development of malignant cancer for this population.

MSAC noted that, in its pre-MSAC response, the applicant agreed with ESC's view that the yield from subsequent scans is likely to be lower than for the baseline scan and stated that it would work with the Department to generate data on incremental yield via the existing SMOC+ study, and then use these observations to define the optimal duration of time between scans. Relevant data could include rates of missed cancers detected between WBMRI scans and if possible, impacts on mortality. MSAC noted more generally that, as this application is the first whole-body MRI item being proposed for individuals with cancer predisposition, some 'future proofing' would be judicious, as other cancer predisposition syndromes will have a lower lifetime risk and hence may not be acceptably cost effective.

MSAC noted that the Department will monitor usage of the item following implementation and, if an unexpected level of item usage is identified, will work with relevant stakeholders to refine the MBS item descriptor to better define the population.

4. Background

MSAC has not previously considered WBMRI for detection of cancer in individuals with pathogenic or likely pathogenic germline variant of *TP53*. The proposed item is for a small, defined population with a rare condition. With the rapid evolution in gene technology resulting in the earlier identification of rare genetic conditions, the Department expects to receive future MSAC applications for similar small patient populations with a high clinical need for diagnostic services but not necessarily the strength of research data to support these services.

5. Prerequisites to implementation of any funding advice

It was noted by PASC that there is no universally accepted definition for WBMRI and advice was 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.

RANZCR advised that there are many ways of acquiring WBMRI depending on the underlying purpose. "Whole-body" strictly refers to a study from the vertex of head to the soles of feet. While some indications require IV contrast, it is generally avoided in screening studies.

All WBMRI studies are acquired in multiple stages (i.e. imaging the head and neck, progressing to the chest, then to the abdomen/pelvis, and finally the lower limbs). In order to maintain image quality, 6 stations are typical for an average person, although this can range from 4 to 7 dependent on patient height. Each stage requires a variety of sequences which are generally a combination of transverse and coronal planes. Sagittal views may be used if the spine is of particular clinical interest.

Studies can take anywhere from 45-90 minutes dependent on patient size and scanner equipment, although 60-70 minutes would be a reasonable average. As eligible patients can have a large number of cancers due to the defective tumour suppressor gene, a systematic search through all sequences takes from 1-2 hours depending on how many abnormalities are found.

6. Proposal for public funding

The proposal is for a new MBS listing for WBMRI. The proposed item is presented in Table 1, and reflect changes to the initially proposed item descriptor to (i) remove the age limit to those aged 65 years or less (based on advice from the Department) and (ii) use the preferred term "heritable *TP53*-related cancer (h*TP53*rc) syndrome". WBMRI is limited to carriers of pathogenic or likely pathogenic germline variant in the *TP53* gene. The use of WBMRI is limited to once per year and requires a specialist or consultant physician in consultation with a clinical geneticist in a familial cancer or genetic clinic to request WBMRI.

Table 1   Proposed MBS item descriptor for surveillance of patients with pathogenic or likely pathogenic germline variant of the *TP53* gene

Category 5 – Diagnostic Imaging Services
MBS item *XXXX Magnetic Resonance Imaging—whole-body scan for the early 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 has a high risk of developing cancer malignancy due to heritable *TP53*-related cancer (h*TP53*rc) syndrome Restricted to one scan per 12 months
Fee: $1,500.00

The requested fee of $1,500 was not justified by the applicant, but was supported by stakeholders including RANZCR. This fee compares with MRI scans of the head $336.00-$403.20 (which takes an estimated 20-30 minutes) and MRI scans of both breasts of $690 (estimated time of 30-45 minutes).

An individual to be eligible for a WBMRI will be required to have previously had a genetic test to diagnose them as carriers of a germline pathogenic or likely pathogenic variant in the *TP53* gene.

The population description in the MBS has not been adjusted to reflect the narrowing of the population to "carriers of pathogenic or likely pathogenic germline variants in *TP53*, who have either never had a cancer diagnosis, or have had a prior cancer treated systemically with curative intent more than 2 years previously and who remain disease-free" due to the term "disease free' of cancer being a subjective assessment by the clinician without any objective measures. Additionally, the purpose of WBMRI is to detect new primary cancers that current cancer risk management regimens are not designed to detect. As such, new cancers can be detected in these patients by the current cancer surveillance regimen or by WBMRI. Therefore, the efficacy of continuing surveillance with WBMRI after a diagnosis of cancer, in an individual patient, is best left to the treating clinician.

7.   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 and have either never had a cancer diagnosis, or have had a prior cancer treated systemically with curative intent more than two years previously and who remain disease free. Given that pathogenic or likely pathogenic germline variants of the *TP53* gene have autosomal dominant inheritance and are highly penetrant, carriers are considered the at-risk affected population.

There is only one PICO set. WBMRI will be used in addition to current technology usually after current cancer risk management options but may be used concomitantly. The population as outlined above is narrower than that described in the PICO, by the addition of requiring that the patients have either never had a cancer diagnosis, or have had a prior cancer treated systemically with curative intent more than two years previously, and who remain disease free.

The difference between the current and the proposed clinical management algorithm is the addition of WBMRI to the surveillance of individuals with a clinically actionable pathogenic or likely pathogenic germline variant of *TP53*. In terms of the proposed clinical management pathway, WBMRI will sit alongside other cancer risk surveillance options. It is not anticipated that there will be any differences in how these individuals are managed *per se*, but that earlier detection will enable earlier access to these management options.

The DCAR of WBMRI for surveillance of patients with a pathogenic or likely pathogenic *TP53* variant addresses most of the PICO elements that were prespecified in the PICO confirmation that was ratified by PASC. As described above the population has been narrowed to require that eligible patients are cancer free after two years of being treated systemically with curative intent.

8.   Comparator

The nominated comparator is current cancer risk management in individuals with germline pathogenic *TP53* variants, which are standard MBS-funded management options. The proposed intervention, WBMRI, would be in addition to this current cancer risk management. It has been noted that standard cancer risk management in this condition is complex, evolving and patient specific.

The standard MBS-funded management options include annual physical examination, annual breast MRI from age 20 for women, prophylactic mastectomy, annual brain MRI (for children) as well as 2-5 yearly colonoscopy from age 20 and 2-5 yearly upper gastrointestinal tract endoscopy from age 25.

9.   Summary of public consultation input

Input was received from eight (8) individuals and the following seven (7) 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)
- Genetic Health Queensland
- Parkville Familial Cancer Centre & Peter MacCallum Cancer Centre

Feedback was supportive of the application for public funding of 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 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 national and international guidelines.
- Early detection of inherited cancers may limit the cancer burden on affected individuals and their families.

Consultation feedback suggested the disadvantages of the proposed testing were:

- long WBMRI examination time
- the cost associated with attending additional appointments including loss of income, particularly for those in rural or remote communities
- potential psychological impacts (e.g. anxiety associated with scanning)

- the potential for false positives
- individuals with implants or devices that are contraindicated/unsafe in a magnetic field would be excluded from the service.

A further comment received in consultation feedback was that MSAC could consider the inclusion of other syndromes with increased risk of cancer such as Lynch Syndrome or those with *BRCA1* and *BRCA2* pathogenic variants. The applicant agreed and stated that this is seen 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.

10. Characteristics of the evidence base

Table 2   Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied		Overall risk of bias in evidence base
Direct from test to health outcomes evidence	1 RCT; 1 prospective observational comparative study	☒	k=2 n=194	High – RCT High – comparative study
Accuracy and performance of the test	8 diagnostic accuracy studies (1 meta-analysis of diagnostic accuracy studies; 7 single-arm observational studies)	☒	k=8 n=1008	High/unclear
Change in patient management	1 RCT; 1 prospective observational comparative study, 8 diagnostic accuracy studies (1 meta-analysis of diagnostic accuracy studies; 7 single-arm observational studies)	☒	k=10 n=1202	High/unclear
Health outcomes	1 prospective observational comparative study and 3 meta-analyses	☒	k=4 n=3809847	High – comparative study Low – meta-analyses

k=number of studies, n=number of patients; RCT=randomised controlled trial

11. Comparative safety

Generally, studies reported that WBMRI was safe and acceptable due to the avoidance of radiation exposure, which is particularly important for the LFS population who are at higher risk of developing cancers.

Caron (LIFSCREEN 2017) reported that "[p]sychological impact was similar in both arms, with low screening-related distress". Rippinger (2020)[17] and LEAD (Ross 2017)[18] qualitatively explored the themes around WBMRI surveillance in LFS patients. Perceived benefits from WBMRI plus standard surveillance included the early detection of cancers, peace of mind, and information from surveillance. Having cancers detected early or at least having knowledge of cancer status

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[17] Rippinger N, et al. (2020). 'Cancer surveillance and distress among adult pathogenic TP53 germline variant carriers in Germany: A multicenter feasibility and acceptance survey', *Cancer*, **126**(17):4032-4041.

[18] Ross J, et al. (2017). 'The psychosocial effects of the Li-Fraumeni Education and Early Detection (LEAD) program on individuals with Li-Fraumeni syndrome', *Genetics in Medicine*: official journal of the American College of Medical Genetics, **19**(9):1064-1070.

was highlighted to reduce cancer worry and distress in LFS patients. Perceived drawbacks of surveillance included logistical issues, such as the extensive time commitments and travel, as well as the physical and emotional burden of attending screening examinations.

A further point of concern for Australian patients may be that although guidelines recommend WBMRI as part of surveillance, the absence of funded screening could be a source of distress.

The addition of WBMRI appears unlikely to lead to worse safety outcomes compared with standard surveillance alone as observed by the non-inferior psychological impact in LIFSCREEN[1] and supported by Rippinger (2020), Ross (2017), SIGNIFY[19], and SMOC+.

An additional point of concern was the routine use of contrast agents (CA) with WBMRI for screening, which is highly discouraged. Petralia (2021) reported long-term gadolinium deposition in the brain (Guo 2018) and possible adverse effects in patients with undisclosed acute kidney injury (Schieda 2018) as reasons to avoid CA administration. In addition, the discomfort related to intravenous injection might also deter patients from undergoing the examination. Studies in the LFS population have used CA in protocols that included a dedicated brain MRI in the same sitting of WBMRI, therefore requiring CA administration (Mai 2017[20] and LEAD[21]). However, as brain MRI is not routinely performed in *TP53* variant adults in the Australian setting (advice from the applicant), concerns with administering CA are reserved for children with LFS.

12. Comparative effectiveness

A direct evidence approach was used (see Section 2B.1), supplemented by a linked evidence approach (see Sections 2B.2 to 2B.4) given bias, methodological and applicability concerns with the direct evidence.

Direct evidence

The direct evidence presented in the DCAR consisted of:

- One randomised controlled trial, LIFSCREEN, assessing annual WBMRI plus standard cancer surveillance (n=52) compared to standard cancer surveillance alone (n=53) in detecting new primary cancers and reporting patient outcomes (i.e., overall survival) in individuals with a pathogenic or likely pathogenic germline *TP53* variant; and
- One observational comparative study (Villani 2016, 2011) comparing standard cancer surveillance (including WBMRI) versus no surveillance in patients with pathogenic or likely pathogenic *TP53* variants. Villani (2016, n=89) represented an extended follow-up and additional patient accrual compared with Villani (2011, n=33). The surveillance protocol was also updated between publications with the addition of general assessments (physical examination every 3-4 months) for adults and children and surveillance of adrenocortical carcinoma by abdominal-pelvic ultrasound for adults in Villani (2016).

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[19] Bancroft EK, et al. (2020). 'Psychosocial effects of whole-body MRI screening in adult high-risk pathogenic TP53 mutation carriers: a case-controlled study (SIGNIFY)', Journal of Medical Genetics, 57(4):226-236.

[20] Mai PL, et al. (2017). 'Prevalence of Cancer at Baseline Screening in the National Cancer Institute Li-Fraumeni Syndrome Cohort', JAMA Oncology, 3(12): 1640-1645.

[21] Bojadzieva J, et al. (2018). 'Whole body magnetic resonance imaging (WB-MRI) and brain MRI baseline surveillance in TP53 germline mutation carriers: experience from the Li-Fraumeni Syndrome Education and Early Detection (LEAD) clinic', Familial Cancer, 17(2):287-294.

Patients enrolled in LIFSCREEN and Villani (2016, 2011) were both consistent with those for whom MBS listing is sought; participants were required to have a known pathogenic or likely pathogenic germline *TP53* variant. Similarly, the surveillance programmes in both the trial and study were also consistent with Australian standard surveillance, although patients underwent breast ultrasound (LIFSCREEN), abdominal-pelvic ultrasound (LIFSCREEN; Villani 2016, 2011) and adults had routine brain MRI (LIFSCREEN; Villani 2016, 2011), which are not features of Australian standard surveillance.

LIFSCREEN was considered to have a high risk of bias due to neither patients nor investigators being blinded to surveillance allocation, not all outcomes (e.g., quality of life) being reported and due to the relatively small sample size and short follow-up and likely being underpowered to detect a difference in patient outcomes. Villani (2016, 2011) was considered to be at a high risk of bias given the study was not randomised (patients chose surveillance versus no surveillance, introducing confounding related to the potential systematic differences in characteristics of participants in each group), neither patients nor investigators were blinded to surveillance strategy, patients could cross-over at any time and analyses were conducted on an as-treated basis.

The diagnostic accuracy estimates from LIFSCREEN are presented in Table 3. The results account for the presence of two lesions in two patients that were not detected by WBMRI (one myeloma 8 months after a normal WBMRI, one jaw osteosarcoma 4 months after the last WBMRI) and treat them as false negatives in the STD+WBMRI group as they were reported to have been 'missed by WBMRI' in Caron (unpublished), but were not reported as interval cancers.

Table 3 Sensitivity, specificity, PPV, and NPV in the STD arm and STD+WBMRI arm in *TP53* variant carriers over 3 years (LIFSCREEN)

LIFSCREEN	STD[a]	STD+WBMRI[b]
Diagnostic yield per screening episode, %	4.97%[a]	5.73%[b]
Sensitivity	0.62	0.82
Specificity	0.74	0.61
PPV	0.17	0.14
NPV	0.96	0.98

NPV=negative predictive value; PPV=positive predictive value
[a]   assuming 161 scans
[b]   assuming 157 scans
Source: based on data in Table 22 of DCAR

In LIFSCREEN, the addition of WBMRI to standard surveillance increased the diagnostic yield compared to standard surveillance (5.73% versus 4.97%, respectively). The sensitivity of a regimen containing WBMRI was also higher, with reduced specificity. Although LIFSCREEN provided estimates of the diagnostic accuracy of both a surveillance strategy that included WBMRI or not, the estimates are not directly comparable as they are derived from surveillance strategies conducted in different patients with different cancers. This is contrary to usual estimations of diagnostic accuracy of a test to detect a cancer (in this example) if it is present in a particular individual.

In order to provide an estimate of the diagnostic accuracy of STD in the STD+WBMRI arm of the trial, further estimations were conducted. The applicant provided analyses of the cancers detected in LIFSCREEN, indicating which of the cancers observed in the STD+WBMRI would have been detected by current Australian surveillance (see Table 8). Eleven or nine (including or excluding the two lesions in two patients that were not defined as interval cancers, respectively) new primary cancers were detected in the STD+WBMRI arm of the trial. Of these, nine cancers

were detected by WBMRI and four would have been detected by current modalities relevant to the Australian setting. Estimates of diagnostic accuracy based on this information are presented in Table 4.

Table 4 Sensitivity and specificity of current Australian standard surveillance in the STD+WBMRI arm in *TP53* variant carriers (LIFSCREEN)

LIFSCREEN	STD[a]	STD+WBMRI[b]
Diagnostic yield per screening episode	2.54%[a]	5.73%[a]
Sensitivity	0.36	0.82
Specificity	0.58	0.61

[a]   assuming 157 scans
Source: based on data in Table 27 of DCAR

These analyses demonstrate a more than doubling of the diagnostic yield, increased sensitivity and specificity with the addition of WBMRI to standard surveillance. A similar trend was also observed for the STD arm of the trial, see Table 8.

The overall survival estimates reported in LIFSCREEN and Villani (2016, 2011) are presented in Table 5 and Table 6, respectively.

Table 5 3-year overall survival (OS) in the STD arm and STD+WBMRI arms in LIFSCREEN

LIFSCREEN	STD	STD+WBMRI
Survived, n/N (%)	49/53 (92)	48/52 (92)
3-year OS, % (95% CI), p-value	89 (75-96), p=0.58	91 (77-97), p=0.58
3-year OS after cancer, % (95% CI)	61 (31-85)	47 (18-78)

CI=confidence interval; OS=overall survival; STD=standard surveillance alone, STD+WBMRI=standard surveillance plus whole-body magnetic resonance imaging
Source: Caron, unpublished; Caron 2018

Table 6 Summary of overall survival (3-year and 5-year) of the surveillance arm compared to no surveillance

Villani 2016, 2011	Surveillance	No surveillance
Survived at end of first follow-up, n/N (%), p-value	7/7 (100), p=0.0417	2/10 (20), p=0.0417
3-year OS, % (95% CI), p-value	**100 (NR), p=0.0155**	**21 (4-48), p=0.0155**
Survived at end of last follow-up, n/N (%), p-value	16/19 (84), p=0.012	21/43 (49), p=0.012
5-year OS, % (95% CI), p-value	**88.8 (78.7-100), p=0.0132**	**59.6 (47.2-75.2), p=0.0132**

NR=not reported
Source: Villani 2016 p1298, Villani 2011 pp561-2

The 3-year overall survival of the STD and STD+WBMRI was similar and no statistically significant differences were observed between surveillance strategies in LIFSCREEN (Table 5). It is possible that the addition of WBMRI to standard cancer surveillance does not improve overall survival. It is also possible that no statistically significant differences were observed due to the (i) small sample size, (ii) the relatively short follow-up in this population that continues to be predisposed to developing cancer and (iii) the types of cancer developed by patients over the trial duration.

A survival benefit in those who underwent cancer surveillance compared to those who did not was observed at 3-years (Villani 2011) and at 5-years (Villani 2016). Although Villani (2016, 2011) did not include an appropriate comparator arm, the study does provide some information about the benefit of cancer surveillance and treatment at detection rather than if the cancer was identified once symptomatic (as per the no surveillance group). Confounding associated with the study sample is likely present in Villani (2016, 2011) due to the non-randomised and self-

selected cohort. This has the potential to impact the timing of those who receive treatment and therefore exaggerate survival outcomes.

The addition of WBMRI has been recommended in domestic and international guidelines (Kratz 2021[22], Hanson 2021[23], Frebourg 2020[24], Consul 2021[25], and Ballinger 2015[26]) as a more comprehensive screening modality that could detect a broader spectrum of cancers that would not be picked up otherwise by standard of care surveillance alone. Despite the limited interpretation of cancer types and stage of cancer at detection in LIFSCREEN and Villani (2016, 2011), it is possible that the proposed benefit of adding WBMRI to surveillance has been missed due to the methodological issues identified in these studies. The paucity of robust evidence has also been noted in current guidelines where "it was recognised that due to the rarity of LFS and *TP53* PVs [pathogenic variants], there is, and likely always will be, a limited evidence base to support screening recommendations in terms of early detection and cancer mortality" (Hanson 2020, pp138). Generally, guidelines have relied upon limited evidence supplemented by expert judgement when recommending the most appropriate surveillance regime. Intuitively, the addition of WBMRI may result in more cancer types being detected early, however, it will be important for protocols to be updated as future studies using larger and more representative samples arise. However, these additional trials are unlikely to be undertaken given ethical issues and because guidelines already recommend the inclusion of WBMRI as part of standard surveillance protocols.

Linked evidence

Diagnostic accuracy

Studies reporting cumulative cancer detection were recognised to provide more meaningful results (and allow estimates for sensitivity as measures for false negatives were available) compared to studies reporting baseline results only, given the proposed annual and ongoing surveillance nature of the test.

One trial (LIFSCREEN, see above) and three studies (SMOC+, Paixao 2018, and O'Neil 2018 [who screened only children]) provided cumulative cancer detection data of WBMRI + standard cancer surveillance. The results for the three studies are presented in Table 7.

[22] Kratz CP, et al. (2021). 'Overview of the Clinical Features of Li-Fraumeni Syndrome and the Current European ERN GENTURIS Guideline', Geburtshilfe und Frauenheilkunde, 82(1):42-49.

[23] Hanson H, et al. (2021). 'UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variants', Journal of Medical Genetics, 58(2):135-139.

[24] Frebourg T, et al. (2020). 'Guidelines for the Li–Fraumeni and heritable TP53-related cancer syndromes', European Journal of Human Genetics, 28(10):1379-1386.

[25] Consul N, et al. (2021). 'Li-Fraumeni Syndrome and Whole-Body MRI Screening: Screening Guidelines, Imaging Features, and Impact on Patient Management', AJR Am J Roentgenol. 216(1):252-263.

[26] Ballinger ML, et al. (2015). 'Surveillance recommendations for patients with germline TP53 mutations', Curr Opin Oncol. 27(4):332-7.

Table 7   Summary of diagnostic accuracy – sensitivity, specificity, PPV, and NPV (SMOC+, Paixao 2018, O'Neil 2018)

	Patients	Lesions
SMOC+		
Diagnostic yield, %	16.67%	6.38%
Sensitivity	0.95	0.95
Specificity	0.58	0.47
PPV	0.22	0.16
NPV	0.99	0.99
Paixao 2018		
Diagnostic yield, %	5.08%	2.54%
Sensitivity	1.00	1.00
Specificity	0.86	0.93
PPV	0.27	0.27
NPV	1.00	1.00
O'Neil 2018		
Diagnostic yield, %	0.00%	0.00%
Sensitivity	NA	NA
Specificity	0.70	0.87
PPV	NA	NA
NPV	1.00	1.00

NPV=negative predictive value; PPV=positive predictive value

Test sensitivity was high in *TP53* variant adults as demonstrated in SMOC+ and Paixao (2018), indicating WBMRI to be reliable in detecting true cases of new primary cancers in this population. Although sensitivity values trended similarly, the confidence in test sensitivity is unclear. The rate of false negative cases was low in these studies, which might be attributable to an insufficient median follow-up window to detect any interval cancers with the median follow-up periods for SMOC+ and Paixao (2018) being unclear.

The specificity of WBMRI varied across these studies, with SMOC+ demonstrating the lowest specificity (0.47) and Paixao (2018) and O'Neil (2018) having a specificity of 0.93 and 0.87, respectively. This is consistent with the nature of WBMRI being a broad surveillance modality, therefore, while there may be a greater number of clinically significant lesions detected, many may eventuate as benign or normal findings.

One meta-analysis (Ballinger 2017; included SMOC+, Paixao 2018, O'Neil 2018, SIGNIFY, and Mai 2017) and four cross-sectional studies (SIGNIFY, LEAD, Mai 2017, LifeGuard[27]) reported diagnostic accuracy on baseline WBMRI scans. Ballinger (2017) reported a diagnostic yield of 7% (95% CI: 5-9%) based on the number of patients presenting one or more new primary cancers. No significant differences between gender or age on diagnostic yield were found. The specificity (0.94) was high in this study, suggesting that WBMRI has the ability to detect true negative findings. However these findings are according to baseline scans. Interval findings were not reported in two other studies (Mai 2017 and LifeGuard), therefore determining reliable sensitivity values was not possible. For studies that did report incidental findings (SIGNIFY and LEAD), the sensitivity values were 0.67 and 0.70, respectively. WBMRI diagnostic yield in other studies

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[27] Ruijs MWG, et al. (2017). 'Surveillance of Dutch Patients With Li-Fraumeni Syndrome: The LiFe-Guard Study', JAMA Oncology, 3(12):1733-1734.

ranged between 3.57% and 13.21% and specificity in these studies ranged between 0.59 and 0.76.

Change in management

The addition of WBMRI to a cancer surveillance programme is intended to (i) identify cancers in areas of the body that are not currently undergoing active surveillance and/or (ii) identify cancers earlier (e.g. when asymptomatic). The increased detection of lesions may also result in additional testing to confirm the status of the tumour (i.e, benign versus malignant).

Analysis of the types of cancers detected across all studies included for diagnostic accuracy indicated brain, soft-tissue, and breast tumours were the most commonly identified cancers, followed by bone, lung, thyroid, and kidney cancers.

Further analyses of the cancers detected in LIFSCREEN were provided by the applicant. This analysis made judgments regarding whether there was clinical utility in early detection, and whether the tumour would have been detected by WBMRI, other modalities used in standard cancer surveillance in Australia and by ultrasound (a modality used in LIFSCREEN, but not in Australia). Table 8 presents this analysis for new primary cancers detected in LIFSCREEN; grey shaded cells represent tumours that would have been identified by WBMRI but not by any other standard Australian surveillance modality and black shading indicates tumours that were not treated with curative intent, implying late-stage disease.

Table 8   New primary cancers detected in LIFSCREEN – detected by WBMRI, detected by current Australian surveillance

Diagnosis	Clinical value in early detection	Detectable by WBMRI?	Detectable by SoC Australian setting?	Detectable by ultrasound?	Treated with curative intent?
STD+WBMRI					
Choriocarcinoma (metastatic)	Yes	Yes	No	Possibly	Yes
Breast	Yes	Yes	Breast MRI	No	Yes
Glioblastoma (<18 years)	Yes	Yes	Brain MRI	No	Yes
Glioma (<18 years)	Yes	Yes	Brain MRI	No	Yes
Adrenocortical carcinoma	Yes	Yes	No	Possibly	No
Lung	Yes	Yes	No	No	Yes
Breast	Yes	Yes	Breast MRI	No	Yes
Lung	Yes	Yes	No	No	Yes
Lung	Yes	Yes	No	No	Yes
STD					
Bladder carcinoma	Yes	No	Urinalysis	Yes	Yes
Pancreas	Yes	Yes	No	Possibly	No
Colon (interval cancer)	Yes	Maybe	Faecal occult blood test	No	Yes
Glioma (adult)	Yes	Yes	No	No	Yes
Sarcoma	Yes	Yes	No	No	Yes
Breast	Yes	Yes	Breast MRI	No	Yes
Lung (interval cancer)	Yes	Yes	No	No	No
Glioma (<18 years)	Yes	Yes	Brain MRI	No	Yes
Kidney	Yes	Yes	No	Possibly	Yes
Sarcoma (interval cancer)	Yes	Yes	No	No	Yes
Breast	Yes	Yes	Breast MRI	No	Yes
Lung (interval cancer)	Yes	Yes	No	No	No
Breast (interval cancer)	Yes	Yes	Breast MRI	No	Yes

Source: LIFSCREEN data V2 excel workbook

The analysis indicates there are a number of tumours (of different histologies) that would not have been detected by any of the modalities in current Australian cancer surveillance strategies in both arms, noting that three of seven (43%) such cancers in the standard surveillance arm of the trial were indeed 'missed' by surveillance and presented as interval cancers (false negatives). One of nine (11%) cancers in the STD+WBMRI arm compared with three of 13 (23%) cancers in the STD arm were not treated with curative intent.

Additional testing for confirmation of whether detected lesions were benign or malignant tumours from the included studies were also reported. From the included studies, a total of 1431 WBMRI scans were performed of which approximately 41% resulted in additional follow-up tests conducted. On average, 23% (of the 41%) of additional tests led to a new primary cancer diagnosis, with the remainder (77%) resulting in a benign or normal outcome. Further data from the applicant from the SMOC+ study indicated that following baseline and subsequent WBMRI, 26.2% and 16.4% of the additional testing resulted in a confirmation of a new primary cancer, respectively, with all other testing confirming either (i) a recurrence or metastases (not the purpose of WBMRI) or (ii) benign neoplasms or normal anatomic variations. Although the MBS listing for WBMRI is neither proposed for monitoring cancer recurrence during the two-years period following systemic treatment, nor response to treatment, this is valuable information for a patient. Also, over time, it would be expected that the number of additional tests performed for

"normal anatomic variations" would decrease as past WBMRI results could be compared and a lesion that was confirmed previously wouldn't be subjected to additional testing repeatedly.

Health outcomes

The diagnostic accuracy of WBMRI plus standard cancer surveillance in the *TP53* germline variant population has been shown to have high sensitivity (i.e., is proficient in identifying tumours), and may detect cancers that would otherwise go undetected until symptomatic or detect cancers at an earlier (i.e. curative) stage. Thus, evidence to support superior patient outcomes (overall survival) from cancer treatment initiated at an earlier versus a later stage was sought.

No evidence directly investigating cancer treatment initiated at an earlier versus a later stage in patients with pathogenic or likely pathogenic *TP53* germline variants was identified. However, Villani (2016, 2011) provided evidence to inform the overall survival of patients with germline *TP53* variants with a tumour diagnosed symptomatically (in the non-surveillance group) versus one diagnosed by surveillance. As reported above, the surveillance group demonstrated statistically significant improvements in overall survival.

To further supplement this, a further three meta-analyses (Johnson 2021[28], Hanna 2020[29], and Mhaskar 2010[30]) were identified, each considered early versus late curative cancer treatment on overall survival and all were considered to have a low risk of bias. Each of these included patients from the general population, however the applicant confirmed it was reasonable to expect patients who are diagnosed with cancer undergo the same routine treatment (with the exception of radiation therapy, if it could be avoided) and would expect similar outcomes regardless of *TP53* germline variant status. The results from the meta-analyses are presented in Table 9.

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[28] Johnson BA, et al. (2021). 'A systematic review and meta-analysis of surgery delays and survival in breast, lung and colon cancers: Implication for surgical triage during the COVID-19 pandemic', American Journal of Surgery, 222(2):311-318.

[29] Hanna TP, et al. (2020). 'Mortality due to cancer treatment delay: systematic review and meta-analysis', BMJ (Clinical research ed.), 371.

[30] Mhaskar AR, et al. (2010). 'Timing of first-line cancer treatments - early versus late - a systematic review of phase III randomized trials', Cancer Treatment Reviews, 36(8):621-628.

Table 9   Results of overall survival of delayed versus earlier cancer treatment across a range of cancer indications in Johnson 2021, Hanna 2020, and Mhaskar 2010

Study	Delay period	Studies	Cancer type	HR (95% CI)	I^2, p-value
Johnson 2021	12-weeks	11	Breast - non-stage specific	**1.46 (1.28-1.65)**	86%, p<0.01
		5	Breast - Stage I	**1.27 (1.16-1.4)**	97%, p<0.01
		5	Breast - Stage II	**1.13 (1.02-1.24)**	89%, p<0.01
		3	Breast - Stage III	1.20 (0.94-1.53)	63%, p<0.07
		5	Lung	**1.04 (1.02-1.06)**	84%, p<0.01
		7	Colon	**1.24 (1.12-1.38)**	71%, p<0.01
Hanna 2020	4-weeks	3	Bladder	**1.06 (1.01-1.12)**	53%, p=0.12
		6	Breast	**1.08 (1.03-1.13)**	94%, p=0
		2	Colon	**1.06 (1.01-1.12)**	0%, p=0.48
		2	Head and neck	**1.06 (1.04-1.08)**	0%, p=0.95
		2	NSCLC	1.06 (0.93-1.19)	54%, p=0.14
Mhaskar 2010	Symptomatic presentation	4	Prostate	**1.23 (1.11-1.37)**	0%, p=0.99
		1	Lung	0.95 (0.72-1.24)	NA
		2	Chronic lymphocytic leukemia	0.76 (0.56-1.04)	0%, p=0.74
		3	Multiple myeloma	0.92 (0.56-1.52)	41%, p=0.18
		2	Follicular lymphoma	1.00 (0.55-1.83)	16%, p=0.28

All studies performed a random-effects model. Comparator was no treatment delay or earlier treatment (HR=1).
CI=confidence interval; HR=hazard ratio; NA=not applicable; NSCLC=non-small cell lung cancer

The meta-analyses indicated that a delay in cancer surgery or first-line treatment led to an increased risk of death.

Intervening with earlier cancer treatment i.e., at an earlier stage or asymptomatic diagnosis, can be reasonably assumed to improve survival outcomes in LFS patients. However, the range of cancers covered by the survival evidence does not adequately reflect the types of cancers applicable to LFS.

Clinical claim

The use of WBMRI plus standard cancer surveillance results in uncertain comparative effectiveness compared with standard cancer surveillance alone in individuals with a pathogenic or likely pathogenic *TP53* germline variant in terms of overall survival. Although the LIFSCREEN trial did not report any statistically significant improvements in overall survival, it is possible that no statistically significant differences were observed due to the (i) small sample size, (ii) the relatively short follow-up in this population that continues to be predisposed to developing cancer and (iii) the types of cancer developed by patients over the trial duration.

The results need to be considered in conjunction with the observation that adding WBMRI to a surveillance regimen increased the diagnostic yield and the sensitivity of the regimen to correctly detect more cancers. Further analysis of the LIFSCREEN data also demonstrated that a number of cancers that were identified when WBMRI was included in the regimen would not have otherwise been detected by current standard Australian surveillance regimens.

The use of WBMRI plus standard cancer surveillance results in noninferior safety compared with standard cancer surveillance alone in individuals with a pathogenic or likely pathogenic *TP53* germline variant.

In its pre-ESC response, the applicant noted the reliance on the LIFSCREEN study for clinical effectiveness and to underlie the cost effectiveness analysis, based on the randomised prospective nature of this study, but pointed out that it had the following flaws:

- There is a significant imbalance between the standard and intervention arms of this study. The study included 8 cancers that are not detectable by imaging methods, and which should therefore have been evenly distributed across both arms (4 basal cell carcinomas, 3 acute leukemias and a myeloma).Yet 7/8 of these were identified in the control arm, suggesting that this population may be more cancer prone, which therefore may explain the greater than expected number of cases diagnosed by imaging. The applicants considered that this may in part explain why the study remains unpublished.
  - In its rejoinder, while the Assessment Group acknowledged the limitations of the LIFSCREEN trial, it observed that LIFSCREEN was the only study to report an estimate of the diagnostic characteristics of the comparator (although it also acknowledged that the comparator differed from standard surveillance in Australia). The Assessment Group further noted in its rejoinder that it attempted to adjust for the imbalances between screening arms in the separate analyses based on the applicant's further analysis of the LIFSCREEN data.

- The study was not adequately powered, nor did it have long enough follow-up, to detect differences in overall survival. The median survival from metastatic sarcoma is 2 years, and for breast cancer significantly longer. By contrast, Villani (2016) although not randomised, did show a striking difference in overall survival. The applicants noted that while Villani (2016) probably overstates the survival benefit, given the length of follow up, it constitutes the best available study on the effect of the intervention on overall survival. The applicants further noted that a survival benefit was not required for approval of the item for breast MRI for women at high risk of breast cancer.
  - The Assessment Group acknowledged that the lack of an overall survival benefit in LIFSCREEN may have been due to factors related to the trial rather than there being no real difference. However the Assessment Group observed that while Villani (2016) demonstrated an overall survival benefit, this was based on comparing surveillance to no surveillance at all, which is not representative of current standard Australian practice.

In its pre-ESC response, the applicant noted that after the LIFSCREEN study was completed, the WBMRI was endorsed as a routine part of surveillance for the Li-Fraumeni population (Frebourg 2020),

The applicant in its pre-ESC response provided some additional evidence for early detection at more curable stages of disease by comparing results from the Australian and New Zealand Sarcoma Alliance (ANZSA) Accord dataset of bone and soft tissue sarcoma diagnoses which suggested that 11 -17% of sporadic sarcomas are diagnosed at a resectable or curable stage in the community with results from the SMOC+ study which found that of 5 WBMRI-based diagnoses of sarcomas, all were localised at diagnosis and the meta-analysis by Ballinger et al (2017) which identified 13 additional WBMRI-based diagnoses of sarcomas, all localised at diagnosis. Based on this overview the applicant concluded that 18 individuals have been diagnosed with sarcoma based on WBMRI, all of which are localised (p=0.057 comparing with the ANZSA data). The applicant noted that these data are consistent with the available data for breast cancer for size of tumors at diagnosis in screening programs linked to survival outcomes for breast cancer. The applicants argued that given the heterogeneity of cancer diagnoses in the LFS population, these are the best estimates of down-staging due to screening. The Assessment Group in its rejoinder noted that it had not been able to verify the new data cited from ANZSA given time limitations.

13. Economic evaluation

Superiority in overall survival in the *TP53* variant population of WBMRI plus standard surveillance compared with standard surveillance alone was not demonstrated by the "direct from test" clinical evidence presented from LIFSCREEN.

However, the results of the diagnostic accuracy WBMRI plus standard surveillance versus standard surveillance alone from LIFSCREEN demonstrated that a surveillance regimen that includes WBMRI improves diagnostic yield and has greater sensitivity.

Table 10 presents a summary of the features of the economic evaluation based on the LIFSCREEN trial.

In addition, to aid contextualisation of ICERs using measures of effectiveness other than QALYs, the Department of Health has developed a summary of MSAC past decisions on genetic testing where related denominators of the ICERs were expressed in terms other than cost per life year or quality adjusted life years gained.

Table 10 Summary of the economic evaluation based on the LIFSCREEN accuracy estimates

Component	Description	Comments
Perspective	Health care system perspective	Excluding out-of-pocket expenses
Population	LIFSCREEN trial patients who have tested positive for a pathogenic or likely pathogenic germline variant of the *Tumor Protein 53* (*TP53*) gene	Source: LIFSCREEN trial data including the diagnostic yield, which was used as the prior probability in Bayesian revision formulae.
Prior testing	Genetic testing to confirm germline pathogenic *TP53* variant status	The associated costs are common to the intervention and comparator arms and not included in the economic evaluation.
Comparator	Standard Australian current surveillance protocol for the *TP53* population	There were discrepancies in the LIFSCREEN trial protocol and Australian current surveillance protocol for the *TP53* population.
Type(s) of analysis	Cost-effectiveness analysis	
Outcomes	Estimated number of correct diagnoses in STD+WBMRI and STD arms	Only new primary cancers were counted (i.e. occasions of relapses were excluded).
Time horizon	One year	Although the median follow-up was 3.2 years in both arms of LIFSCREEN (Caron 2018), the data have been applied in the economic evaluation as if collected over a one-year period.
Computational method	Arithmetic calculations using Bayes theorem and Bayesian revision formulae	
Generation of the base case	Diagnostic test accuracy data (sensitivity and specificity) obtained from the LIFSCREEN trial	Depending on the underlying assumptions, there was more than one way of estimating sensitivity and specificity, which produced alternative primary ICERs and sensitivity analyses.
Health states	Not applicable	
Cycle length	Not applicable	
Transition probabilities	Not applicable	
Discount rate	Not applicable	
Software	TreeAge Pro	TreeAge Pro was not used for modelling purposes, only for the convenience and accuracy of Bayesian revision calculations.

TP53=*Tumor Protein 53*; WBMRI=Whole-body magnetic resonance imaging; STD=Standard cancer surveillance

The cost-effectiveness analyses produced a number of ICER estimates for the incremental cost per additional correct diagnosis, namely new primary cancer correctly detected given positive test results and new primary cancer correctly ruled out given negative test results. Only incremental costs were included. The total annual cost of adding WBMRI to the standard surveillance protocol is estimated at $1561 and consists of $1500 (cost of the WBMRI procedure) plus $61 (additional investigations per lesion due to the false positive results of the scan).

The first primary ICER (Table 11) utilises the LIFSCREEN diagnostic accuracy data reported in Table 3.

Table 11 Summary of results using the accuracy estimates based on the observed true positives, true negatives, false positives and false negative results in each arm of the LIFSCREEN trial (Table 3)

Health technology alternatives	Costs ($)	Incremental cost ($)	Outcomes (+ve NPCs correctly identified)*	Incremental outcome	ICER ($/+ve NPC correctly identified)*	Outcomes (-ve NPCs correctly ruled out)*	Incremental outcome	ICER ($/-ve NPC correctly ruled out)*
WBMRI + surveillance	1561	1561	0.1183	-0.0138	STD dominates	0.9815	0.0133	117,825
Surveillance only (STD)	0		0.1321			0.9682		

WBMRI=whole-body magnetic resonance imaging; NPC=new primary cancer detected or ruled out; +ve=positive; -ve =negative
*   Over the duration of the LIFSCREEN trial of "at least 3 years" (Caron, 2018)

The results indicate that with respect to correctly identifying a new primary cancer (given a positive test result) a surveillance program including WBMRI was dominated by the comparator. In the corresponding arithmetical calculations, a compliment of specificity (1-specificity) is entered in the denominator. Therefore, the lower specificity of WBMRI+STD than STD alone is reflected in the negative value of incremental outcome. With respect to correctly ruling out a negative primary cancer (given a negative test result), the reverse is true, since it is a complement of sensitivity (1-sensitivity), which is in the denominator, therefore favouring WBMRI+STD with its sensitivity being greater than the comparator's. The corresponding ICER is estimated at $117,825 per negative new primary cancer correctly ruled out (given a negative test result). Values for PPV and NPV in Table 11 slightly differ to those reported in Table 3 as they are estimated using Bayesian revision formulae and explicitly include the estimate of the prevalence of cancer (based on the diagnostic yield observed in the LIFSCREEN trial). Epidemiologically, the values of PPV and NPV vary with the population prevalence, therefore inclusion of this parameter allows for sensitivity analysis to assess variability of PPV and NPV when varying estimates of prevalence. There is a potential source of bias in the accuracy estimates as these were derived from two different populations defined by the randomisation. In the small-sample trial, randomisation was likely insufficient to ensure that the distribution of patients over the most common cancers in the *TP53* variant population was comparable in the intervention and comparator arms. In addition, WBMRI is associated with the higher detection rate in identifying particular types of cancers, namely soft-tissue and bone tumours that would not be detected by standard surveillance protocols. Therefore, the comparable presentation of these types of cancer was essential for reducing the possible source of bias.

To overcome this problem, a hypothetical exercise was conducted by recalculating the diagnostic accuracy estimates. As discussed above, further analyses of the cancers detected in LIFSCREEN were provided by the applicant. This analysis made judgments regarding whether the tumour would have been detected by WBMRI or other modalities used in standard cancer surveillance in Australia (see Table 8). In the hypothetical exercise, only the patients from the WBMRI+STD arm of the LIFSCREEN trial were considered and assumed to be subjected to both protocols, i.e., with and without WBMRI. Expert opinion regarding whether the tumour would have been detected by

current Australian standard surveillance in the population that was randomised into WBMRI +STD arm was used. Table 8 shows that assuming that the same population was tested with the surveillance protocol with and without WBMRI, inclusion of WBMRI would detect five additional lesions (9-4) for the same number of WBMRI scans (N=157).

The hypothetical exercise has effectively revised the number of true positives and true negatives in the STD arm producing the new diagnostic accuracy estimates (see Table 4). Table 12 summarises the results for the second primary ICER applying Bayesian revision formulae to the re-estimated values of sensitivity and specificity from the hypothetical exercise.

Table 12 Summary of results using the accuracy estimates based on the recalculated number of true positives cancer detected by STD in the group that had STD+WBMRI, in WBMRI+STD arm of the LIFSCREEN trial

Health technology alternatives	Costs ($)	Incremental cost ($)	Outcomes (+ve NPCs correctly identified)*	Incremental outcome	ICER ($/+ve NPC correctly identified)*	Outcomes (-ve NPCs correctly ruled out)*	Incremental outcome	ICER ($/-ve NPC correctly ruled out)*
WBMRI + surveillance	1561	1561	0.1183	0.0664	23,494	0.9815	0.0473	33,007
Surveillance only (STD)	0		0.0519			0.9342		

WBMRI=whole-body magnetic resonance imaging; NPC=new primary cancer detected or ruled out; +ve=positive; -ve=negative
*   Over the duration of the LIFSCREEN trial of "at least 3 years" (Caron, 2018)

The results estimate ICERs for a surveillance program including WBMRI of $23,494 per new primary cancer correctly identified and $33,007 per negative new primary cancer that was correctly ruled out. Both estimates are conditional on the positive and negative test results, respectively. Comparing results in Table 11 and Table 12, and notwithstanding the small sample size and the subjective nature of the expert's opinion, it is evident that addition of WBMRI to the standard cancer surveillance protocol, would produce dramatically lower estimates of the incremental cost per correct diagnosis.

Table 13 summarises results of the sensitivity analyses where the value of a prior probability (prevalence of cancerous lesions in the *TP53* population), assumed to be 6% in the CEAs reported above was varied using the estimates of 3.57% and 13.21% which represent the lowest and highest estimates of WBMRI diagnostic yields (used as prevalence estimates) from studies reporting baseline data.

Table 13 Sensitivity analysis for the value of the prevalence (prior probability) of the cancerous lesions in the *TP53* population

Prevalence of cancer assumed	Sensitivity / specificity	ICER ($/+ve NPCs correctly identified)*	ICER ($/-ve NPCs correctly ruled out)*
6% (base case Table 3)	STD+WBMRI 0.82 / 0.61 STD 0.62 / 0.74	STD dominates	117,825
3.57% (Table 45 of the DCAR)			195,153
13.21% (Table 45 of the DCAR)			53,535
6% (both protocols in the same population from WBMRI+STD arm Table 4)	STD+WBMRI 0.82 / 0.61 STD 0.36 / 0.58	23,494	33,007
3.57% (Table 45 of the DCAR)		38,079	55,758
13.21% (Table 45 of the DCAR)		12,293	15,457

WBMRI=whole-body magnetic resonance imaging; NPC=new primary cancer detected or ruled out; +ve=positive; -ve=negative
*   Over the duration of the LIFSCREEN trial of "at least 3 years" (Caron, 2018)

Sensitivity analyses shows that results are very sensitive to the variations in the value of population prevalence. Assumptions about the higher prevalence are associated with lower ICER values in the scenarios where the same population from WBMRI+STD arm was hypothetically subjected to both protocols (with and without WBMRI). Increasing the prevalence from 3.57% to 13.21% decreased ICER estimates by approximately a factor of three. In the population analysed according to the randomisation outcomes, STD remained dominant with respect to the incremental cost per additional new primary cancer correctly diagnosed regardless of the assumptions about the population prevalence. This is suggestive of results being very sensitive to the difference in the diagnostic accuracy between the surveillance that includes WBMRI and the comparator of the standard cancer surveillance only. However, with respect to the incremental cost per additional cancer correctly ruled out given the negative test result, increasing the prevalence from 3.57% to 13.21% decreased the ICER estimates from $195,153 to $53,535.

Results of economic evaluations depend on numerous assumptions, of which the most important relates to the LIFSCREEN trial populations that provided evidence for the accuracy estimates. Base case results in the populations analysed according to randomised groups are not comparable to the results of the hypothetical exercise, where the same population of the WBMRI+STD arm was subjected to the surveillance protocol with and without WBMRI. This is because, according to the expert's advice, some of the cancers cannot be detected by STD alone, necessitating re-estimation of sensitivity and specificity, which favoured WBMRI+STD protocol over the comparator of the standard cancer surveillance.

The purpose of diagnostic testing is to move from the probability of disease before the diagnostic test (prior probability) to the probability after the diagnostic test based on the test result (posterior probability or positive predictive value). Irrespective of the test properties (sensitivity and specificity) Bayes' rule shows that if prior probabilities change, so do different posterior probabilities, which is reflected in ICER estimates that decrease in proportion to the increase in the positive predictive value.

14.   Financial/budgetary impacts

The financial implications to the MBS over 6 years resulting from the proposed listing of WBMRI for surveillance of patients with a clinically actionable germline pathogenic or likely pathogenic *TP53* variant are summarised in Table 14.

The factor determining the size of the eligible population, is patients having received a molecular test that determines they have heritable *TP53*-related cancer syndrome. The availability of this test is not part of this assessment. Information about the proportion of the carrier population that have accessed this test is unknown. Therefore, two baseline analysis were conducted:

1) A financial analysis of the estimate of the population provided by the applicant (assuming a 10% growth in population for each year), this population is based on the applicant's expert advice on the take-up of surveillance by high risk patients, see Table 14; and
2) A financial estimate of the likely population based on the estimated carrier population and their uptake of WBMRI (includes those with a diagnosis and those yet to have a diagnosis). This analysis is based on prevalence data from Gonzalez (2009)[31] as that most likely representative of prevalence of heritable *TP53*-related cancer syndrome in the Australian population (based on Question 49 of the application). These estimates are higher but are presented to validate the estimates provided in the application and to provide information

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[31] Gonzalez K, et al. (2009). 'Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations', Journal of Clinical Oncology, 27(8): 1250-1256.

about the financial implications if the population is greater than estimated in the application, see Table 15.

Table 14 Net financial implications of WBMRI to the MBS—first financial analysis

	2021-22	2022-23	2023-24	2024-25	2025-26	2026-27	
Population (≥18 years) <18 years	250 80	275 88	302 97	333 106	366 117	403 139	Application
Population growth	**0**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	10% growth (estimate)
Total population	330	363	399	439	483	531	
Cost	$495,000	$544,500	$598,950	$658,845	$724,730	$797,202	MBS fee $1500
Net cost	**$465,993**	**$512,592**	**$563,852**	**$620,237**	**$682,260**	**$750,486**	**MBS fee $1500 - GPG $87.90**

GPG=greatest permissible gap

Table 15 Net financial implications of WBMRI to the MBS—second financial analysis

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of the proposed health technology						
Number of people eligible for WBMRI	1069	1196	1196	1196	1196	1196
Number of people who receive WBMRI	658	739	739	739	739	739
Number of services of WBMRI (if more than one per person)	N/A					
Cost of WBMRI (with appropriate co-payments [GPG] excluded)	$929,315	$1,043,889	$1,043,889	$1,043,889	$1,043,889	$1,043,889
Change in use and cost of other health technologies						
Change in use of MBS items	$85,731	$18,639	$18,639	$18,639	$18,639	$18,639
Change in use of further investigations	N/A					
Net change in costs to MBS (with appropriate co-payments excluded, assume 0.85)	$72,871	$15,843	$15,843	$15,843	$15,843	$15,843
Net financial impact to the MBS	**$1,002,186**	**$1,059,731**	**$1,059,731**	**$1,059,731**	**$1,059,731**	**$1,059,731**

GPG=greatest permissible gap; MBS=Medicare Benefits Schedule; WBMRI=whole-body magnetic resonance imaging

The estimated financial implications relied on the following:

- The average cost of WBMRI per patient per year is $1,412.10 (MBS Fee of $1,500 minus the greatest permissible gap (GPG) of $87.90).
- The average frequency of use of WBMRI is once per year.
- If the WBMRI is bulk billed, then there will be no cost to the patient. If it requires a co-payment, then the patient is required to pay $87.90/year.

The estimated likely eligible population for WBMRI is greater than that in the application.

The second financial analysis estimated the potential prevalence of heritable *TP53*-related cancer syndrome in both the paediatric and adult population. It assumed that being an identified

carrier would result in surveillance for cancer in a one-to-one relationship. This is unlikely to occur as patients first need to be identified by molecular testing, be of age for which annual surveillance has benefit, agree to ongoing surveillance and either to have not yet had a cancer or to have a prior cancer being treated with curative intent. This analysis also included an average cost of follow up investigations for benign tumours.

The applicant's pre-ESC submission noted that one way to accommodate the uncertainty in projections of use is to approve the application subject to ongoing data collection, similar to what was undertaken for breast MRI in women at high risk for breast cancer, with a review of the uptake in 3-5 years' time with the option to further refine the item description and explanatory guidance material at this time. The Department proposes to undertake ongoing review of the item usage following implementation, and work with relevant stakeholders where higher or lower than expected item usage is identified

15. Other relevant information

None.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Proposed MBS fee and item descriptor:

The MBS item descriptor should specify *TP53* variants

The proposed fee of $1,500 seems high relative to MBS fees for other MRI items but may be reasonable if account is taken of reporting time as well as examination time. However no justification of the fee has been provided by the applicant. The possibility of a lower fee for children has not been explored, The proposed fee is supported by RANZCR due to the time requirements and complexity of this service.

Clinical evidence issues:

Local and international clinical practice guidelines recommend the use of WBMRI in the defined patient population as this modality supports more comprehensive surveillance, detecting a broader spectrum of cancers than is possible with standard of care surveillance (without imaging). However it should be noted that these are consensus recommendations rather than evidence-based recommendations. Because of the challenge of collecting robust evidence given the rarity of the syndrome, there is, and likely always will be, a limited evidence base to support screening recommendations in terms of early detection and cancer mortality.

Safety:

MRI surveillance is generally safe and acceptable as it does not rely on ionising radiation. However, in the context of this population who are likely to undergo multiple MRI examinations, the use of gadolinium as a contrast agent needs to be limited due to the potential long-term accumulation of gadolinium deposition in the brain and the kidneys with uncertain long-term consequences.

Economic issues:

While the base case ICER in the DCAR is similar in value to ICERs previously accepted by MSAC for genetic and genomic testing, it is based on a slightly different definition of diagnostic yield.

While there are limitations in the dataset relied on in the DCAR to generate the ICER and the financial estimates, additional data are unlikely to emerge given the general paucity of robust clinical data (as identified earlier).

While ESC accepts the approach in the DCAR of reporting ICERs on a per scan basis, it was acknowledged that there may be diminishing marginal value *per patient* scanned over time if new cancers tend to emerge in earlier years of scanning. Additional evidence regarding the natural history of new primary cancers emerging over time in the defined population would be needed to address this possibility (the key studies in the DCAR are not sufficiently powered to provide year by year estimates of cancer detection rates). However, this would be difficult to measure in practice as (i) *TP53*-positive individuals would be entering and leaving the surveilled cohort each year, and (ii) the emergence of *TP53*-associated cancers is age-dependent and differs by cancer type.

Financial issues:

Despite the high MBS fee per WBMRI, the low prevalence of the syndrome means that the total impact to the MBS budget is modest. The requirement for prior genetic testing means the likelihood of utilisation outside the intended indication is close to zero.

Other relevant information:

The current limited availability of testing for *TP53* variants (affected individual and cascade) on the MBS needs to be addressed.

The addition of WBMRI screening to standard screening regimens needs coordination and planning to integrate with physical examination, breast screening, ultrasound imaging, colonoscopies and gastroscopies.

This application is for a very limited population with a rare genetic cancer predisposition which is associated with a very high lifetime risk of developing various cancers.

ESC discussion

ESC noted that the application was for 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 *TP53* gene for the early detection of cancer.

ESC noted that germline pathogenic variants in the *TP53* gene cause Li Fraumeni Syndrome (LFS), a rare condition affecting between 1 in 5,000 and 1 in 20,000 of the population which is associated with higher cancer risk. In particular, this patient population has a very significant clinical need for surveillance for the early detection of cancer as they have a greater than 90% chance of developing cancer in their lifetime, the highest of all cancer predisposition syndromes. ESC noted that while *TP53* is the only gene that has been definitively associated with LFS, not all people with a *TP53* variant will have LFS.

ESC noted that the proposed intervention, WBMRI, would be in addition to current cancer risk surveillance options which for this condition are complex, evolving and patient specific.

ESC noted that this application initially sought to list an annual WBMRI scan to detect cancer in asymptomatic individuals aged 18 years and over with germline pathogenic *TP53* variants. However, at its August 2021 meeting, PASC recommended that the population be expanded to include children with germline pathogenic *TP53* variants (under 18 years).

ESC noted that the applicant's claim is that annual surveillance with WBMRI will result in earlier detection of malignant lesions, and that subsequent earlier treatment will improve patient outcomes. ESC noted that the earlier detection and treatment facilitated by annual WBMRI

surveillance may lead to overall lower treatment costs and faster recovery for patients. However, there are also costs associated with attending additional appointments for the WBMRI scan which could result in loss of income, particularly for those in rural or remote communities.

ESC noted that, currently, some germline *TP53* testing is accessible via the MBS through items 73296 and 73297 for individuals suspected of hereditary breast and ovarian cancer (HBOC), as *TP53* is one of four genes suspected to increase risk of these cancers. However with the exception of these MBS items there is limited availability of testing for *TP53* variants (affected individual and cascade) on the MBS. *TP53* testing is currently funded by State/Territory genetic services.

ESC noted that the MBS item descriptor in the policy paper currently describes the population as person[s] with "a high risk of developing cancer malignancy due to heritable *TP53*-related cancer (h*TP53*rc) syndrome". This does not yet reflect the proposal discussed between the applicant and Department to limit the eligible population to: "carriers of pathogenic or likely pathogenic germline variants in *TP53*, who have either **never had a cancer diagnosis**, or have had a prior cancer treated systemically with curative intent **more than 2 years previously and who remain disease-free**". However ESC noted that the population description has not been adjusted in the item descriptor because:

- the term "disease free' of cancer is often a subjective assessment by the clinician often without any objective measures
- such a restriction would be inappropriate in this population who need ongoing surveillance even in the context of a recent cancer diagnosis, particularly as they are prone to multi-site malignancies.

The revised descriptor also removes both lower and upper age limits.

ESC noted that the MBS item descriptor should specify the *TP53* variants. Post-ESC, policy noted that one option to address this is to provide guidance on the *TP53* variants in the explanatory notes for requestors.

The Department will monitor the usage of the item following its implementation, and work with relevant stakeholders to further refine the item descriptor if necessary, where higher or lower than expected item usage is identified.

ESC noted that there is a low risk of leakage because the patient population is well-defined.

ESC noted that the applicant did not provide justification for the $1500 fee other than the claim that it takes one hour to perform the scan, though stakeholder feedback supported the proposed fee. ESC noted the advice from RANZCR that the scan also has a lengthy reporting time of at least an hour due to the number of sequences to be reviewed.

ESC noted that currently the highest schedule fee for MRI services is $1,200.00 for fetal MRI, a complex scan which takes a minimum of 45 minutes to complete. ESC noted that based on the lowest and highest fee per minute from MBS items 63001 for brain MRI and 63464 for breast MRI, the full MBS fee for WBMRI would be $805.80 to $1,380.00 for a 60-minute scan. ESC queried if the fee should be lower for children, since the time taken to scan from vertex to the soles of the feet is shorter but the distance between scanning planes is the same. ESC also noted that there is a bulk billing incentive for other MRI items, which may or may not apply to this new item.

ESC noted that the 85% fee accounts for the greatest permissible gap of $87.90. It was noted that neither the application nor Department-contracted assessment report (DCAR) mentions the 75% fee, but this may not be required if the service will not be provided to admitted patients.

ESC noted that as with most MBS-reimbursed MRI services, requesting of the proposed item will be restricted to a specialist or consultant physician in consultation with a clinical geneticist in a familial cancer or genetic clinic.

ESC noted that it is proposed that WBMRI will be provided by a specialist in diagnostic radiology who is a participant in the RANZCR Quality and Accreditation Program. Currently, there are 385 operational MRI units eligible to provide this service through Medicare.

ESC noted that local and international clinical practice guidelines recommend the use of WBMRI in the defined patient population as a more comprehensive screening modality that can detect a broader spectrum of cancers that would not be picked up by standard of care surveillance without imaging. However ESC noted that these are consensus recommendations rather than evidence-based recommendations because of the challenge of collecting evidence given the rarity of the syndrome.

ESC recognised that due to the rarity of LFS and *TP53* pathogenic variants, there is, and likely always will be, a limited evidence base to support surveillance recommendations in terms of early detection and cancer mortality.

ESC noted that MRI is generally safe, as it is non-ionising (critical for a patient population at high risk of developing cancers) and is proven to have equivalent or superior sensitivity and specificity than modalities such as ultrasound and computed tomography for the detection of tumours not arising in a hollow viscus. ESC noted that that perceived benefits from WBMRI plus standard surveillance included the early detection of cancers, peace of mind (beneficial psychological impact) and information from surveillance.

However ESC noted that one additional point of concern for WBMRI was the routine use of contrast agents with WBMRI for screening, which is highly discouraged. Petralia (2021)[32] reported long-term gadolinium deposition in the brain (Guo 2018) [33] and possible adverse effects in patients with undisclosed acute kidney injury (Schieda 2018) [34]. ESC noted that if gadolinium were to be used in WBMRI as well as other standard MRI screening episodes, the total usage of the contrast agent would need to be monitored.

ESC noted that patients with *TP53* pathogenic variants have increased radiation sensitivity due to impaired recognition and repair of DNA damage and there are numerous reports of second primary malignancies developing in areas previously treated with radiation therapy. Minimising radiation therapy is therefore recommended where possible, especially if other treatment modalities with comparable cure rates are available. ESC noted that there is no published study evaluating the potential detrimental effect of ionising radiation (mammography) used for screening purposes in *TP53* pathogenic variant carriers. However, there is a concern about the cumulative risk of mammograms in very young women exposed to mammograms for a long

[32] Petralia G, et al. (2021). 'Whole-body magnetic resonance imaging (WB-MRI) for cancer screening: recommendations for use', *La Radiologia Medica*, **126**(11):1434-1450

[33] Guo BJ, et al (2018). 'Gadolinium Deposition in Brain: Current Scientific Evidence and Future Perspectives', *Front Mol Neurosci.***11**:335.

[34] Schieda N, et al. (2018). 'Gadolinium-Based Contrast Agents in Kidney Disease: Comprehensive Review and Clinical Practice Guideline Issued by the Canadian Association of Radiologists', *Can Assoc Radiol* J. **69**(2):136-150

period of time. Additionally ESC noted that mammograms may be more difficult to interpret in younger women with denser breasts[35][36] so if breast MRI is available for younger women in this patient population it should be used in preference to mammography.

ESC noted that, for clinical effectiveness, a direct evidence approach was used, supplemented by a linked evidence approach, given bias, methodological and applicability concerns with the direct evidence.

ESC noted that four sets of studies formed the evidence base for clinical effectiveness in the application – the LIFSCREEN randomised controlled trial (RCT) [37]; the Villani (2011) [38] and Villani (2016) [39] observational comparative study with 11 years follow up; the Surveillance study in Multi-Organ Cancers (SMOC) reported by SMOC+[40], Paixao (2018) [41] and O'Neil (2018) [42], and the Ballinger (2017)[43] meta-analysis.

ESC noted that the only prospective RCT, LIFSCREEN, had flawed data, was not peer reviewed and was only presented at a conference. LIFSCREEN was also considered to have a high risk of bias due to neither patients nor investigators being blinded to surveillance allocation, not all outcomes (e.g., quality of life) being reported, and the relatively small sample size and short follow-up meaning the study was likely underpowered to detect a difference in patient outcomes.

ESC noted that while LIFSCREEN was designed to evaluate the impact of adding WBMRI as a screening tool on the overall survival (OS) of LFS patients it found no difference between the standard surveillance arm and the standard + WBMRI arm in terms of 3 year OS or cancer free survival. However, as noted previously this may be due to the study being underpowered.

ESC noted that in LIFSCREEN, the addition of WBMRI to standard surveillance increased the diagnostic yield compared to standard surveillance (5.73% versus 4.97%, respectively) and the sensitivity of a regimen containing WBMRI was also higher, though with reduced specificity.

ESC noted that Villani (2016, 2011) was considered to be at a high risk of bias given the study was not randomised (patients chose surveillance versus no surveillance, introducing confounding related to the potential systematic differences in characteristics of participants in each group),

[35] Pinsky RW, et al. (2010). 'Mammographic breast density: effect on imaging and breast cancer risk', *L Natl Compr Canc Netw*, **8**(10): 1157-64.

[36] Bell RJ. (2020). 'Mammographic density and breast cancer screening', *Climacteric*, **23**(5): 460-465.

[37] Caron O, et al. (2017). 'Lung Adenocarcinoma as Part of the Li-Fraumeni Syndrome Spectrum: Preliminary Data of the LIFSCREEN Randomized Clinical Trial', *JAMA Oncology*, **3**(12):1736-1737

[38] Villani A, et al. (2011). 'Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study', *The Lancet Oncology*, **12**(6):559-567

[39] Villani A, et al. (2016). 'Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study', *The Lancet Oncology*, **17**(9):1295-1305

[40] Thomas D and Ballinger M. (unpublished). 'Unpublished data from the Australian SMOC+ whole-body MRI surveillance study in TP53 germline variant carriers'. Provided March 2022.

[41] Paixão D, et al. (2018). 'Whole-body magnetic resonance imaging of Li-Fraumeni syndrome patients: observations from a two rounds screening of Brazilian patients', *Cancer Imaging: the official publication of the International Cancer Imaging Society*, **18**(1):27.

[42] O'Neill AF, et al. (2018). 'Screening with whole-body magnetic resonance imaging in pediatric subjects with Li–Fraumeni syndrome: A single institution pilot study', *Pediatric Blood and Cancer*, **65**(2).

[43] Ballinger ML, et al. (2017). 'Baseline Surveillance in Li-Fraumeni Syndrome Using Whole-Body Magnetic Resonance Imaging: A Meta-analysis', *JAMA Oncology*, **3**(12):1634-1639.

neither patients nor investigators were blinded to surveillance strategy, patients could cross-over at any time and analyses were conducted on an as-treated basis. ESC noted that, subject to these significant caveats, a survival benefit in those who underwent cancer surveillance compared to those who did not was observed at 3-years (Villani 2011) and at 5-years (Villani 2016).

ESC noted that the SMOC studies (SMOC+, Paixao 2018) found high sensitivity of WBMRI in *TP53* adults.

ESC noted that in the Ballinger (2017) meta-analysis the overall estimated detection rate for new, localized primary cancers was 7% (95% CI, 5%-9%) and the false-positive rate was 42.5%.

ESC agreed that in the cost effectiveness analysis, a cost per life years saved approach was not informative based on the direct clinical evidence (given the inconclusive results from the LIFSCREEN trial).

ESC noted that the DCAR derived incremental cost-effectiveness ratios (ICERs) based on shorter term outcomes, namely diagnostic accuracy estimates from LIFSCREEN. ESC noted that examples of such measures from past MSAC applications include incremental cost per [improved] measure of diagnostic yield, and that these ICERs have been used in situations where the condition of interest is rare, and evidence of downstream consequences is absent or very limited. ESC noted that the measure 'incremental cost per extra treatment allocation improvement' was relied on by MSAC for the use of FDG-PET in staging for rare cancers.

ESC noted there were challenges with directly comparing the ICERs from the economic evaluation with ICERs generated for genetic/genomic testing in previous MSAC applications as:

- the latter assumed 100% sensitivity and 100% specificity
- the ICERs for the genetic/genomic testing were based on a different definition of diagnostic yield (all positive test results, i.e. true positives plus false positives).

ESC noted that the DCAR reported the results of cost effectiveness analysis based on two data series. The first relied on data as reported by LIFSCREEN. The second relied on the applicant's re-interpretation of LIFSCREEN data which was reviewed by the assessment group. ESC noted that while neither dataset was ideal, the second series was more applicable from an HTA perspective as it adjusts for current surveillance protocols in Australia. While there are limitations in the dataset relied on in the DCAR to generate the ICER (and the financial estimates), additional data is unlikely to emerge given the general paucity of robust clinical data (as identified earlier).

ESC noted that the key cost input into the economic evaluation was the annual cost of WBMRI as proposed by applicant of $1,500. Added to this was the weighted average annual cost of additional investigations associated with detection of lesions subsequently found to be benign or normal which based on observed resource use in the SMOC study was estimated at $61. ESC noted that the key outcomes of the economic evaluation were expressed in terms of positive new primary cancers (NPCs) correctly identified and negative NPCs correctly ruled out.

ESC noted that the DCAR reported an ICER per positive NPC correctly identified of $23,494 and an ICER per negative NPC correctly ruled out of $33,007 assuming an underlying cancer prevalence of 6%. ESC noted that a sensitivity analysis was undertaken around this baseline assuming a minimum cancer prevalence of 3.57%, resulting in ICER per positive NPC correctly identified of $38,079 and ICER per negative NPC correctly ruled out of $55,758; and a maximum cancer prevalence of 13.21% resulting in ICER per positive NPC correctly identified of $12,293 and ICER per negative NPC correctly ruled out of $15,547.

ESC had questions on whether the specific approach used in the DCAR was appropriate and accordingly sought and received the following clarifications from the assessment group:

- The base case cancer prevalence of 6% (the prior probability of cancer) is a rounding of the diagnostic yield figure of 5.73% in Table 23 of the DCAR.
- The definition of diagnostic yield was the number of new primary cancers detected/total number of scans performed, which can be distinguished from a possible alternative definition of diagnostic yield as the rate of positive findings. Diagnostic yields were calculated separately by trial arm and then the highest value ("6%" as above) was used as the estimate of cancer prevalence (i.e. prior probability of cancer in the defined population) for both arms in the cost effectiveness analysis.
- The diagnostic yield data from the study itself were used to define the prior probability (of cancer prevalence) in the Bayesian approach to the economic analysis because an alternative source, namely Ballinger 2017 reported a 7% cancer detection rate; so the base case assumption of 6% is a conservative estimate within the 95% confidence interval.
  - ESC noted that the assessment group will update the base case using 7% from Ballinger 2017 for methodological completeness, although it is not expected to have any significant financial impact.
  - Post-ESC it is noted that the assessment group has provided in a separate addendum new ICER estimates based on a 7% cancer detection rate and under three different sets of assumptions on WBMRI sensitivity and specificity.
- Because the total number of benign lesions (over the period of the LIFSCREEN trial) was used to estimate sensitivity and specificity, the assessment group considered it appropriate to hold constant the $61 per additional investigation per lesion due to false positive results in all the analyses presented in the DCAR. Moreover the $61 was only 4% of the current cost per investigation of $1561 and therefore the assessment group considered that a sensitivity analysis based on varying this cost component would result in negligible differences in outcomes.
- The economic evaluation used data from the total number of screens over the entire period of the trial to reconstruct unreported true negatives and to inform false negative rates, Based on this approach, the assessment group assumed that the sensitivity and specificity estimates were applicable at any point in time (i.e. at annual testings), thus attracting only the annual cost of $1561.
  - ESC noted that the assessment group will amend Table 61 of the DCAR to reflect the fact that although the median follow-up was 3.2 years in both arms of LIFSCREEN, the data have been applied in the economic evaluation as if collected over a one year period. This also means that discount rates are not applicable in the economic evaluation.
- The outcomes used in column 4 of Tables 63–65 of the DCAR (the positive NPCs correctly identified) are not conventional intermediate outcomes but are conditional probabilities.
  - ESC noted that the DCAR should revised to make this clearer.

While ESC accepted the approach in the DCAR of reporting ICERs on a per scan basis, it was acknowledged that there may be diminishing marginal value *per patient* scanned over time if new cancers tend to emerge in earlier years of scanning. Additional evidence regarding the natural history of new primary cancers emerging over time in the defined population would be needed to address this possibility (the key studies in the DCAR are not sufficiently powered to provide year by year estimates of cancer detection rates). However, this would be difficult to measure in practice as (i) *TP53*-positive individuals would be entering and leaving the surveilled cohort each

year, and (ii) the emergence of *TP53*-associated cancers is age-dependent and differs by cancer type.

ESC noted that, in the pre-ESC response, the applicant re-iterated issues with the LIFSCREEN dataset and unreliability of survival outcomes. The applicant also provided analysis of the ANZ Sarcoma Alliance ACCORD dataset to support the argument of value of WBMRI in downstaging of LFS cancers. The assessment group was unable to verify this new data at the time of the ESC meeting.

ESC noted the financial impact presented in the DCAR was $1,059,731 by Year 6, but that this is based on prevalence of 1 in 20,000. If a prevalence of 1 in 5,000 is used, then the financial impact would be closer to $3,000,000 by Year 6. ESC considered that sensitivity analyses of the financial impact with alternative lower MBS fees (especially for children) would be informative.

ESC noted that the addition of WBMRI screening to standard screening regimes will require coordination and planning to integrate with physical examination, breast screening, ultrasound imaging, colonoscopies and gastroscopies.

17.   Applicant comments on MSAC's Public Summary Document

The applicant (Omico) welcome the opportunity to work with the Department in monitoring WBMRI usage and outcomes.

18.   Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website