Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1372.1 – MRI of the liver for patients with colorectal carcinoma (CRC) with suspected hepatic metastases or patients with suspected hepatocellular carcinoma (HCC) for the purposes of staging

Applicant: **The Royal Australian and New Zealand College of Radiologists (RANZCR)**

Date of MSAC consideration: **MSAC 72nd Meeting, 28-29 March 2018**

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 magnetic resonance imaging (MRI) of the liver for patients with colorectal cancer (CRC) with suspected hepatic metastases or patients with suspected hepatocellular carcinoma (HCC) for the purposes of staging was received from the Royal Australian and New Zealand College of Radiologists (RANZCR) 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 and cost effectiveness, MSAC supported MBS funding for gadolinium-enhanced magnetic resonance imaging with a hepatobiliary contrast agent (GA-MRI) of the liver for:

- patients with known CRC with suspected or proven liver metastases for the purpose of characterisation and intervention planning; and
- patients with known or suspected HCC for the purposes of diagnosis and staging.

MSAC recommended listing an MBS item for each population (metastatic CRC and HCC), with the item descriptors specifying use on only one occasion for diagnostic purposes in any 12-month period. MSAC recommended a consolidated fee of $800 which includes the cost of the contrast agent.

MSAC recommended that these MBS items should be reviewed two years after implementation, with regards to the overall utilisation, the cost of the contrast agent, and whether there are multiple MRIs being performed per patient per year.

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

MSAC recalled the previous application (MSAC Application 1372) was not supported at the July 2015 MSAC meeting due to uncertain effectiveness and cost-effectiveness. MSAC noted that the proposed populations in the current application have been narrowed since the previous application to:

- patients with known colorectal carcinoma (CRC) with suspected or proven liver metastases for the purpose of characterisation and intervention planning (population one); and
- patients with known or suspected hepatocellular carcinoma (HCC) for the purposes of diagnosis and staging (population two).

MSAC noted that the comparator for GA-MRI is contrast-enhanced X-ray computed tomography (CE-CT) in both population groups.

MSAC acknowledged the claim that in both populations GA-MRI can be used to determine the pathology, vascularity and resectability of the cancer. MSAC acknowledged that GA-MRI can potentially avoid biopsy procedures and aid treatment decisions such as staging of cancer, surgical planning (including resection or ablation), or palliative chemotherapy.

MSAC accepted that in patients without known contraindications (such as renal impairment or pregnancy), GA-MRI has non-inferior safety compared with CE-CT.

MSAC noted that there was a lack of good quality studies comparing patient outcomes between GA-MRI and CE-CT and accepted that a linked evidence approach was appropriate.

MSAC considered that GA-MRI had similar specificity to CE-CT when compared with biopsy in the metastatic CRC population with pooled values of 93% (95% confidence interval [CI] 91% to 95%) and 96% (95% CI 93% to 97%), respectively. MSAC considered that GA-MRI had better sensitivity than CE-CT when compared with biopsy for the metastatic CRC population with pooled sensitivity values for GA-MRI and CE-CT of 93% (95% CI 91% to 95%) and 75% (95% CI 71% to 78%), respectively.

MSAC considered that GA-MRI had slightly better specificity than CE-CT when compared with biopsy in the HCC population with pooled values of 96% (95% CI 92% to 98%) and 91% (95% CI 86% to 95%), respectively. MSAC considered that GA-MRI had better sensitivity than CE-CT when compared with biopsy for the HCC population with pooled sensitivity values for GA-MRI and CE-CT at 84% (95% CI 81% to 86%) and 75% (95% CI 72% to 77%), respectively.

MSAC considered that GA-MRI was more sensitive and had at least similar specificity when compared with CE-CT for both populations suggesting better diagnostic accuracy which may lead to earlier treatment and/or changes in management. MSAC noted that the rate of change in management from the use of GA-MRI for the metastatic CRC population and the HCC population were up to 38% and 41%, respectively. MSAC considered that a change in management is likely to lead to better outcomes for both populations through the avoidance of inappropriate surgical procedures and avoidance of incomplete surgical intervention due to unidentified tumours.

Based on the presented evidence, MSAC accepted that GA-MRI has reasonable safety and effectiveness relative to CE-CT in both populations. MSAC noted that the incremental cost effectiveness ratio (ICER) for the metastatic CRC population and the HCC population were

$22,893 per quality-adjusted life year (QALY) and $12,737 per QALY, respectively. MSAC accepted that although there were some uncertainties in the economic modelling, the cost effectiveness of GA-MRI upon sensitivity analysis was still considered acceptable.

Based on current utilisation of CE-CT, MSAC noted that there would be an estimated 11,973 services in year 1 rising to 12,370 services in year 5. MSAC noted that the HCC population would primarily receive GA-MRI without a CE-CT scan. MSAC considered that there would be no substitution of CE-CT with GA-MRI in the metastatic CRC population and considered an estimate of 20% replacement of CE-CT with GA-MRI in the HCC population to be a more realistic upper limit.

MSAC noted that the net cost to the MBS for GA-MRI for both metastatic CRC and HCC would be approximately $44 million over five years and $8.8 million per year. Costs were based upon:

- a 20% replacement of approximately 11,500 services of CE-CT with GA-MRI for the metastatic HCC population;
- a cost offset from the replacement of CE-CT with GA-MRI for the HCC population;
- a consolidated fee of $800 (combined MRI fee of $600 and contrast agent fee of $200); and
- 100% cost shift of public/private patients to the MBS.

MSAC considered that a fee of approximately $600 for the proposed MBS items to be appropriate. MSAC noted this was consistent with the fee for MRI for staging of the pelvis and abdomen for cervical cancer (MBS item 63473; MBS fee $627.40).

MSAC noted that MRI of the liver for these indications would always require a contrast agent. MSAC noted that a separate modification of the MBS items for the use of contrast agent (gadobenate dimeglumine [MultiHance] and gadoxetic acid [Primovist]) had originally been proposed. From the Applicant pre-MSAC response, MSAC was advised that gadobenate dimeglumine (MultiHance) is no longer available in Australia. MSAC noted that the market price for gadoxetic acid (Primovist) is $250.

MSAC recommended a consolidated fee of $800 that covers the cost of the GA-MRI imaging service and the cost of the contrast agent. MSAC recommended that this fee be revisited in two years to ensure that the cost for the contrast agent remains in line with market prices for gadoxetic acid (Primovist) and any other suitable contrast agents that may enter the market.

MSAC recommended separate MBS items for metastatic CRC patients and HCC patients to enable ongoing monitoring of utilisation.

MSAC recommended GA-MRI be restricted to only one service every 12 months for diagnostic purposes. MSAC considered that while there may be some repeat GA-MRI following liver resection, this was likely to be very low.

MSAC acknowledged the applicant's pre-MSAC response that the inclusion of "has confirmed histology" in the proposed item descriptor for population one was confusing as it may imply the need for biopsy results for eligibility to access GA-MRI. MSAC recommended that the item descriptor be amended to eliminate ambiguity regarding patient eligibility.

MSAC advised that MRI machines need a minimum specification of 1.5 Tesla to adequately image the liver. MSAC recommended against including new NK (classification of MRI machines on the 'capital sensitivity' measure) MBS items for liver MRI on the MBS.

MSAC recommended that these MBS items be reviewed two years after implementation, with regards to the overall utilisation, the cost of the contrast agent, and whether there are multiple MRIs being performed per patient per year.

4. Background

At its July 2015 meeting, MSAC considered Application 1372 for MBS listing of MRI of the liver for patients with known extrahepatic malignancy who are being considered by a specialist for hepatic therapies (including but not limited to percutaneous ablation, resection or transplantation); and patients with known focal liver lesions requiring characterisation.

MSAC did not support public funding because of the uncertain clinical effectiveness, and cost effectiveness due to weak data associated with change in clinical management and no translation of imaging performance to improved health outcomes.

The Public Summary Document (PSD) for this application can be found on the MSAC website at www.msac.gov.au.

5. Prerequisites to implementation of any funding advice

All contrast agents for clinical MRI in Australia are gadolinium-based. Gadolinium-based hepatobiliary agents, which are TGA-listed for use in Australia, are gadoxetic acid (Primovist®) and gadobenate dimeglumine (MultiHance®).

In its pre-MSAC response, the applicant advised that Multihance is no longer available in Australia.

MRI devices are included on the Australian Register of Therapeutic Goods (ARTG).

6. Proposal for public funding

Both eligible populations in the resubmission were more restricted in scope than those proposed in the original MSAC Application 1372.

The applicant proposed a fee of $1,200 for this service based on time required in the scanner. In comparison, MRI procedures for the pelvic staging of rectal (Item 63476) and cervical (Item 63470) cancers both carry a Medicare fee for benefit of $403.20, while MRI of the pelvis and upper abdomen for staging of cervical cancer (Item 63473) carries a fee of $627.20.

The use of MRI services is attached to a modifying item (MBS item 63491 with a fee of $44.80) for use of an extracellular contrast agent eligible in current MRI items. The applicant proposed an additional modifying MBS item for the use of a hepatobiliary-specific contrast agent (e.g. gadoxetic acid). The applicant advised that the cost of the most commonly used hepatobiliary contrast agent, Primovist (gadoxetate disodium), is $250 (current market rate), which is proposed to be reimbursed via a separate contrast modifying item, similar to MBS item 63491.

MSAC initially recommended a consolidated fee of $800 which covered the cost of the GA-MRI imaging service and the cost of the contrast agent. At its 1 June 2018 meeting, the

MSAC Executive considered further expert clinical opinion and decided to separate the contrast agent from the new MRI liver items with a revised fee of $550 for the liver MRI items, a new separate hepatobiliary specific contrast agent item with a fee of $250, and that the liver MRI item descriptors should allow practitioners to select an extracellular contrast agent in cases when this was clinically indicated.

The proposed MBS item descriptors for MRI of the liver are presented in Table 1, Table 2, Table 3 and Table 4.

Table 1 Proposed GA-MRI item descriptor for liver MRI Population Group 1 (mCRC)

Category 5 – DIAGNOSTIC IMAGING SERVICES
Note: Benefits are payable on only one occasion in any 12-month period MAGNETIC RESONANCE IMAGING with a hepatobiliary-specific contrast agent, including delayed imaging when performed, performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or consultant physician – multiphase scans of liver for: A patient with known colorectal carcinoma with known, suspected or possible liver metastasis, for the purpose of characterisation or intervention planning, where: · the patient has had a mass lesion detected in the liver on previous CT scanning or ultrasound. For use with HEPATOBILIARY-SPECIFIC CONTRAST AGENT (item XXXXX). If a patient has known or suspected clinical indication/s considered by a specialist or consultant physician to clinically indicate the need for imaging with an extracellular contrast agent, the modifying MRI item 63491 can be used with this item. Bulk bill incentive Fee: $550 Benefit: 75% = $412.50 85% = $467.50 (See para DIQ of explanatory notes to this category)

Table 2 Proposed GA-MRI item descriptor for liver MRI Population Group 2 (HCC)

Category 5 – DIAGNOSTIC IMAGING SERVICES
Note: Benefits are payable on only one occasion in any 12-month period MAGNETIC RESONANCE IMAGING with a hepatobiliary-specific contrast agent, including delayed imaging when performed, performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or consultant physician – multiphase scans of liver for: A patient with known or suspected hepatocellular carcinoma for the purposes of diagnosis or staging where: · the patient has pre-existing chronic liver disease, confirmed by a specialist; and · has an identified hepatic lesion over 10mm in diameter; and · has been assessed as having a Child-Pugh class A or B liver function. For use with HEPATOBILIARY-SPECIFIC CONTRAST AGENT (item XXXXX). If a patient has known or suspected clinical indication/s considered by a specialist or consultant physician to clinically indicate the need for imaging with an extracellular contrast agent, the modifying MRI item 63491 can be used with this item. Bulk bill incentive Fee: $550 Benefit: 75% = $412.50 85% = $467.50 (See para DIQ of explanatory notes to this category)

Table 3 Proposed new item descriptor for liver MRI liver contrast agent

Category 5 – DIAGNOSTIC IMAGING SERVICES
Item XXXXX NOTE: Benefits in Subgroup 22 are only payable for modifying items where claimed simultaneously with MRI services. Modifiers for sedation and anaesthesia may not be claimed for the same service. Modifying item for use with MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the service requested by a specialist or by a consultant. Scan performed: - involves the use of HEPATOBILIARY SPECIFIC contrast agent, as clinically indicated for eligible Magnetic Resonance Imaging items MBS item XXXXX and MBS item XXXXX Bulk bill incentive **Fee**: $250 **Benefit:** 75% = $187.50 85% = $212.50 (See para IN.0.19 of explanatory notes to this category)

Table 4 Existing MRI modifying item for use with liver MRI

Category 5 – DIAGNOSTIC IMAGING SERVICES
Item 63491 NOTE: Benefits in Subgroup 22 are only payable for modifying items where claimed simultaneously with MRI services. Modifiers for sedation and anaesthesia may not be claimed for the same service. Modifying items for use with MAGNETIC RESONANCE IMAGING or MAGNETIC RESONANCE ANGIOGRAPHY performed under the professional supervision of an eligible provider at an eligible location where the service requested by a specialist or by a consultant. Scan performed: - involves the use of contrast agent for eligible Magnetic Resonance Imaging items (Note: (Contrast) denotes an item eligible for use with this item) Bulk bill incentive Fee: $44.80 Benefit: 75% = $33.60 85% = $38.10 (See para IN.0.19 of explanatory notes to this Category)

7. Summary of Public Consultation Feedback/Consumer Issues

The Department received one response from an organisation. The response strongly supported the use of MRI for patients with CRC with suspected hepatic metastases and patients with suspected HCC for the purposes of staging.

8. Proposed intervention's place in clinical management

MRI is well established for the imaging assessment of the liver, it requires use of hepatobiliary contrast agents which are selectively taken up by liver cells and excreted into the biliary tree.

The clinical management algorithms are similar to those in MSAC Application 1372 although, ESC questioned the appropriateness of the algorithm used for population 1 (metastatic CRC).

9. Comparator

For the resubmission, the comparator is multiphase contrast enhanced (CE)-CT for the majority of patients, with additional biopsy in a smaller proportion of patients.

10. Comparative safety

The safety data were reviewed as part of MSAC application 1372 and accepted.

11. Comparative effectiveness

Direct effectiveness

MSAC Application 1372 identified 4 studies on the direct effectiveness (decision impact) of MRI relative to CT in patients with metastatic CRC and 2 studies in patients with HCC; however none of the studies was considered to be of adequate quality to provide the primary evidence for the clinical and economic evaluation.

The literature search update identified one additional study on the decision impact of MRI relative to CT in patients with HCC.

Effectiveness from linked evidence

Accuracy

Patient group 1: patients with known CRC with suspected or possible liver malignancy

The results demonstrated GA-MRI consistently provides superior sensitivity compared to CE-CT. For GA-MRI, sensitivity values ranged from 90% (Schulz et al., 2016) to 100% (Patel et al., 2014), whereas for CE-CT sensitivity ranged from 63% (Muhi et al., 2011) to 85% (Kim et al., 2015). The difference between the 2 tests ranged from 10% (Asato et al., 2017; Kim et al., 2015) to 32% (Muhi et al., 2011). The data across all eligible studies were pooled to provide sensitivity estimates of 93% for GA-MRI and 75% for CE-CT, with a difference of 18%.

Only 2 studies reported specificity results. The data across both studies were pooled to provide specificity estimates of 93% for GA-MRI and 96% for CE-CT, with a difference of 3%. This result would suggest that both tests classify "true" patients in whom resection is not necessary at an equal rate.

Table 5 Summary statistics for GA-MRI compared to CE-CT in patient group 1: patients with known CRC with suspected or possible liver malignancy

Accuracy (k=7)	Index test	Comparator
Sensitivity [95% CI]	0.93 [0.91, 0.95] (n=1178)	0.75 [0.71, 0.78] (n=1187)
Specificity [95% CI]	0.93 [0.91, 0.95] (n=771)	0.96 [0.93, 0.97] (n=705)
Positive predictive value	0.9 (n=1178)	0.87 (n=1187)
Negative predictive value	0.96 (n=771)	0.88 (n=1187)

Patient group 2: patients with suspected HCC

The evidence base for diagnostic accuracy in patients with suspected HCC consisted of 10 studies, including 7 that were included in MSAC Application 1372 and three that were identified in the updated literature search. All studies included patients who were known to have HCC or who were suspected to have HCC on the basis of previous tests. The eligible studies were further limited to those that included patients with suspected HCC, pre-existing chronic liver disease, hepatic lesions > 10 mm and Child-Pugh classification A or B. The

included studies were a mix of retrospective and prospective study designs, and many had a low to moderate risk of bias.

In the 10 included studies, GA-MRI was shown to demonstrate superior sensitivity compared to CE-CT in all but one study (Joo et al., 2017). The studies reported a wide range of sensitivity estimates for both GA-MRI and CE-CT. For GA-MRI, sensitivity values ranged from 60% (Kawada et al., 2010) to 95% (Imbriaco et al., 2017). By comparison, for CE-CT, sensitivity values ranged from 40% (Kawada et al., 2010) to 91% (Toyota et al., 2013). The data across all eligible studies were pooled to provide sensitivity estimates of 84% for GA-MRI and 75% for CE-CT, with a difference of 9%. The results suggested that GA-MRI more accurately identifies liver lesions associated with HCC than CE-CT.

The pooled specificity was 96% for GA-MRI compared to 91% for CE-CT. These results suggested both tests identify patients who do not require treatment for HCC at a roughly equal rate. As was the case for patient group 1, the diagnostic accuracy data presented do not account for the ability of MRI to identify lesions in addition to those already identified by CE-CT in an individual patient.

Table 6 Summary statistics for GA-MRI compared to CE-CT in patient group 1: patients with known CRC with suspected or possible liver malignancy

Accuracy (k=10)	**Index test**	**Comparator**
Sensitivity, [95% CI]	0.84 [0.81, 0.86] (n=1165)	0.75 [0.72, 0.77] (n=1165)
Specificity, [95% CI]	0.96 [0.92, 0.98] (n=575)	0.91 [0.86, 0.95] (n=575)
Positive predictive value	0.97 (n=1165)	0.96 (n=1165)
Negative predictive value	0.83 (n=575)	0.67 (n=575)

Therapeutic efficacy (change in management)

Patient group 1: patients with known CRC with suspected or possible liver malignancy

The evidence base for the decision impact studies in patients with known CRC and suspected liver metastases consisted of 4 studies, all of which had been previously included in MSAC Application 1372 (Cho et al. 2015; Kim et al. 2015b; Patel et al. 2014; Zech et al. 2014). All 4 studies included patients with CRC and known or suspected liver metastases identified on prior ultrasound or CE-CT.

Change in patient management ranged from 8.5% (Kim et al., 2015) to 38.4% (Zech et al., 2014). In the 2 most applicable studies, which included patients who were candidates for resection, the rates of change in patient management were 9.2% (Cho et al., 2015) and 8.5% (Kim et al., 2015). Change in patient management included extended surgical plans, re-allocation to surgery and radiofrequency ablation. Collectively, these results suggest that the superior sensitivity of GA-MRI relative to CE-CT translates to changes in patient management in clinical practice.

Patient group 2: patients with suspected HCC

The evidence base for the decision impact studies in patients with suspected HCC consisted of 2 studies that were included in MSAC Application 1372 (Cha et al., 2014; Yoo et al., 2013), and one study which was identified in the updated literature search (Wang et al., 2016). All 3 studies assessed the impact of additional GA-MRI on management including

diagnosis, staging, and therapeutic decisions for patients with hepatic nodules suspected or known to be HCC.

The proportion of patients experiencing a change in patient management was roughly 40% in the studies by Cha et al. (2014) and Yoo et al. (2013), and 18.9% in the prospective study by Wang et al. (2016). The studies further suggested that GA-MRI was associated with more appropriately targeted treatment of HCC compared with CE-CT. This included the use of radiofrequency ablation (RFA) or trans-arterial chemoembolisation (TACE), avoidance of surgery for unresectable disease and changes to planned resection margins. Collectively, these results suggested that the superior sensitivity of GA-MRI relative to CE-CT translates to changes in patient management in clinical practice.

Therapeutic effectiveness (health benefit from change in management)

Estimates of 5-year survival in different patient groups are presented in Table 7 and Table 8. Based on data used in MSAC Application 1372 (Edge et al., 2009), 5-year overall survival was: 0.85 in patients with CRC and no liver metastases; 0.24 in patients with CRC and resected metastases; and 0.06 in patients with CRC and untreated metastases (palliative care).

Based on data used in MSAC Application 1372 (Altekruse et al., 2012), 5-year overall survival was: 0.47 in patients with HCC who were optimally treated with resection; 0.08 in patients with HCC who were untreated; 0.98 in patients with benign liver lesions. The economic model presented in Section D of the Assessment Report further assumes patients with optimal treatment have better outcomes (survival) than sub-optimally treated patients. Optimally treated patients are those who have had a change to their management plan as a direct result of their GA-MRI results. In this group, it was assumed that survival would be 0.35, the same as the cohort achieving local tumour destruction.

Table 7 5-year overall survival in patients with CRC and suspected liver metastases

Population	5-year overall survival (SE)	Source
No metastases	0.85 (0.01)	AJCC (Edge et al., 2009)
Metastases with resection	0.24 (0.03)	AJCC (Edge et al., 2009)
Inoperable metastases	0.06 (0.04)	AJCC (Edge et al., 2009)

Abbreviations: AJCC, American Joint Committee on Cancer; CRC, colorectal carcinoma

Table 8 5-year overall survival in patients with suspected HCC

Population	5-year overall survival (SE)	Source
Liver transplant	0.84 (0.03)	Altekruse et al., 2012
RFA	0.53 (0.05)	Altekruse et al., 2012
Liver resection	0.47 (0.02)	Altekruse et al., 2012
Local tumour destruction	0.35 (0.03)	Altekruse et al., 2012
No invasive surgery or local tumour destruction	0.08 (0.0)	Altekruse et al., 2012
Benign lesions	0.98	ABS life tables

Abbreviations: HCC, hepatocellular carcinoma; RFA, radiofrequency ablation

Clinical Claim

The applicant claimed that GA-MRI is superior in safety and effectiveness compared to CE-CT. It was also noted that MRI will be more costly. There may be some savings associated with MRI in terms of reduced inappropriate surgery or avoided adverse events from biopsy, CT or avoided surgery. The appropriate economic evaluation is therefore a cost-utility analysis using a decision analytic model with information on the accuracy of testing, the impact of testing on decision-making, and treatment outcomes including quality of life.

12. Economic evaluation

A summary of the key characteristics of the economic evaluation is shown in Table 9.

Table 9 Summary of the economic evaluation

Perspective	Health care system	
Comparator	CE-CT	
Type of economic evaluation	CUA	
Sources of evidence	Systematic review of prospective, retrospective and clinical trials	
Time horizon	Five years	
Outcomes	Costs QALYs Incremental cost per QALY gained	
Methods used to generate results	Markov cohort analysis	
Health states	**Population 1** Operable mCRC; Undergoing evaluation Inoperable mCRC; Undergoing evaluation No mCRC; Undergoing evaluation Operable mCRC; True positive Operable mCRC; FN Inoperable mCRC; True positive Inoperable mCRC; FN No mCRC; TN Dead	**Population 2** HCC; Undergoing evaluation No HCC; Undergoing evaluation HCC; True positive; Optimally treated HCC; True positive; Sub-optimally treated HCC; FN; Untreated No HCC; TN Dead
Cycle length	Six months	
Discount rate	5 percent per annum	
Software packages used	TreeAge Pro 2017	

For model 1, at a modelled MBS fee of $500, additional costs of $491 per patient and QALY gains of 0.0214 per patient results in an ICER of $22,893. For model 2, additional costs of $654 per patient and QALY gains of 0.0514 per patient results in an ICER of $12,737.

The ICERs in populations 1 and 2 at the applicant's requested MBS fee of $1200 increase to $46,953 and $41,189, respectively.

Table 10 Results: Incremental cost-effectiveness of MRI in each population At PICO confirmed MBS fee of $500 [and applicant requested fee of $1200]

Model	Item	GA-MRI	CE-CT	Incremental
Economic model 1: Patient population with known CRC with suspected or possible liver malignancy	Cost [at applicant fee of $1200]	$12,989.02 [$13,504.77]	$12,498.30	$490.72 [$1,006.47]
	QALYs	1.8283	1.8069	0.0214
	IC/QALY gained [at applicant fee of $1200]			**$22,893 [$46,953]**
Economic model 2: Patient population with suspected HCC	Cost [applicant fee of $1200]	$4,253.97 [$5,715.97]	$3,599.48	$654.50 [$2,116.49]
	QALYs	2.7887	2.7373	0.0514
	IC/QALY gained [at applicant fee of $1200]			**$12,737 [$41,189]**

The key drivers of model 1 and 2 are presented in Table 11 and Table 12 respectively. For model 1, the model was most sensitive to the prevalence of operable liver metastases, and the probability of confirmatory biopsies. For model 2, the model was most sensitive to the decision impact of GA-MRI, the prevalence of HCC, and the 5-year survival of optimally treated HCC relative to sub-optimally treated HCC.

Table 11 Key drivers of the economic model (model 1)

Description	Method/Value	Impact
	0.3 (Wierring, 2011)	Moderate
5-year survival for operable/inoperable liver metastases	Operable liver metastases = 0.24 Inoperable liver metastases = 0.06 (AJCC – Edge et al, 2009)	Moderate
Confirmatory biopsy rates	75% (Kim, 2015)	Moderate to high

Table 12 Key drivers of the economic model (model 2)

Description	Method/Value	Impact
	Treated HCC = 0.75 Untreated HCC = 0.64 (Chong 2003)	Moderate
5-year survival for optimally treated HCC (relative to sub-optimally treated HCC)	Optimally treated HCC = 0.47 Sub-optimally treated HCC = 0.35 (Altekruse 2012)	Moderate to high

13. Financial/budgetary impacts

The financial implications of funding GA-MRI in the resubmission were calculated by updating the estimates in MSAC Application 1372, and ensuring that only the relevant population and comparators were considered.

The original application used a market share approach, due to the wide range of potential diseases (primary cancers with potential liver metastases and primary liver tumours (both malignant and benign) requiring assessment of the liver MRI. The approach was considered appropriate and is replicated in the current resubmission.

The financial implications to the MBS resulting from the proposed listing of MRI are summarised in Table , under a range of possible utilisation scenarios.

The costs are increased beyond CE-CT replacement by GA-MRI by the shift of GA-MRI public hospital/private patients to the MBS. These will be significant further costs to the MBS in addition to the cost of the CE-CT services replaced by GA-MRI services as estimated in Table 13.

Table 13 Net costs to the MBS associated with GA-MRI, by expected level of uptake and substitution of CT services

	Uptake of MRI				
Extent of CT substitution	**100%**	**80%**	**60%**	**40%**	**20%**
100%	$3,755,516	$3,004,413	$2,253,310	$1,502,206	$751,103
80%	$4,448,842	$3,559,074	$2,669,305	$1,779,537	$889,768
60%	$5,142,168	$4,113,735	$3,085,301	$2,056,867	$1,028,434
40%	$5,835,494	$4,668,395	$3,501,297	$2,334,198	$1,167,099
20%	$6,528,820	$5,223,056	$3,917,292	$2,611,528	$1,305,764
0%	$7,222,146	$5,777,717	$4,333,288	$2,888,859	$1,444,429

14. Key issues from ESC for MSAC

ESC noted that this was a resubmission of an application for gadolinium-enhanced magnetic resonance imaging (GA-MRI) of the liver that MSAC did not support in July 2015 due to

uncertain effectiveness and cost-effectiveness due to weak data associated with change in clinical management and no translation of imaging performance to improved health outcomes (MSAC Application 1372). ESC noted that the populations in the submission had been narrowed to:

- patients with suspected hepatic metastases from colorectal cancer (CRC); and
- staging of patients with suspected hepatocellular carcinoma (HCC).

ESC noted that use of the clinical management algorithm for population 2 from MSAC Application 1372 (patients with known focal liver lesions requiring characterisation) was only partially relevant for the metastatic CRC population, and only for those patients in whom a hepatic lesion had been identified on initial staging, usually with computed tomography (CT).

ESC noted that the clinical algorithm for population 1 from MSAC Application 1372 (patients with extrahepatic malignancy and suspected liver metastases being considered for hepatic therapies) should have been used (with modification) instead because it implied that extrahepatic metastases had already been excluded by other means, such as positron-emission tomography with computed tomography (PET/CT).

ESC noted there are no significant safety concerns when using GA-MRI in appropriately selected patients.

ESC noted that the data on the diagnostic accuracy of GA-MRI for the metastatic CRC population drew from seven observational studies considered to be at moderate to high risk of bias. ESC noted that GA-MRI appeared to be more sensitive than contrast enhanced CT (CE-CT; pooled sensitivities of 93% and 75%, respectively) and have similar specificity (pooled specificity of 93% and 96%, respectively) for the metastatic CRC population.

ESC noted that the evidence from four observational studies indicated that GA-MRI changed management in 8.5% to 38.4% of patients in the metastatic CRC population (Cho ES et al 2015; Kim HD et al 2015; Patel J et al 2014; Zech CJ et al 2014).

ESC noted that in the HCC population, there were 10 studies identified for diagnostic accuracy of GA-MRI. However these studies had a moderate to high risk of bias and significant heterogeneity. ESC noted that GA-MRI appeared to have better sensitivity than CE-CT (pooled sensitivities of 84% and 75%, respectively) and have slightly better specificity (pooled specificities of 96% and 91%, respectively) for the HCC population.

ESC noted that three observational studies indicated that GA-MRI changed management in 18.9% to 41.2% of patients in the HCC population (Cha DI et al 2014; Yoo SH et al 2013; Wang JH et al 2016).

ESC considered that the economic model structures for both the metastatic CRC and HCC populations were appropriate.

ESC noted that the incremental cost-effectiveness ratio (ICER) was $22,893 per quality adjusted life year (QALY) for the metastatic CRC population and $12,737 per QALY in the HCC population. ESC noted that this was based upon a GA-MRI fee of $500 with GA-MRI substituting CE-CT. ESC noted that there were a number of uncertainties in the model including:

- the use of international data that may not accurately reflect the background prevalence of resectable hepatic CRC metastases or primary HCC in the Australian population;

- insufficient information on the number and management of patients with indeterminate results.

ESC considered that complete substitution of CE-CT by GA-MRI is unrealistic and the extent to which GA-MRI will replace or be used in addition to CE-CT in both populations is unclear. CE-CT comparator item can also be used for spleen and biliary imaging. In the absence of granular data policy welcomes any guidance on the most likely replacement percentage to use in the range of cost scenarios presented, noting the unrealistic 100% replacement of CE-CT, plus the 100% shift of hospital/private services to the MBS, is presented as an improbable worst-case MBS/Budget cost scenario.

ESC noted that the base case ICER increased to $40,000 for the metastatic CRC population and to $28,000 for the HCC population when it was assumed that all patients received both GA-MRI and CE-CT (but assumed that diagnostic utility and health outcomes were unchanged).

ESC queried the proposed MBS fee of $1200, noted the fee of $500 applied in the economic model, and suggested that a $600 fee — similar to MBS item 63473 for MRI of the pelvis and upper abdomen — may be more appropriate. ESC noted that the applicant is willing to consider a lower fee than $1200.

ESC noted that the application had not included information on the use of standard (extracellular) rather than hepatobiliary contrast agents. ESC considered that the item descriptor for the supplementary modifying agent should specify the use of hepatobiliary specific contrast agents such as disodium gadoxetate (Primovist) or gadobenate dimeglumine (Multihance) rather than extracellular agents such as gabutrol (Gadovist).

ESC foreshadowed that the use of gadobenate dimeglumine (Multihance) could lead to two separate GA-MRI services being billed due to the delay in peak hepatobiliary accumulation of contrast agent. Peak hepatocellular uptake of disodium gadoxetate (Primovist) occurs approximately 16 minutes after administration as opposed to 90–120 minutes for gadobenate dimeglumine (Multihance). ESC considered that the item descriptor should cover both early and delayed phase GA-MRI to prevent the possibility of two billings. .

ESC noted that while a separate item descriptor for the contrast agent had been proposed, no associated fee has been proposed. ESC noted that the current market price of disodium gadoxetate (Primovist) is $250 and gadobenate dimeglumine (Multihance) is approximately $20. ESC noted that there is an existing MBS item 63491 for the use of contrast agent with an associated fee of $44.80, and if this item is used there is the potential the MBS may pay a higher price than is reasonable for the gadobenate dimeglumine (Multihance) contrast agent.

ESC also noted that there are concerns that consumers may be exposed to out of pocket costs if the proposed modifying agent fee is inadequate. ESC noted that there is an international trend towards a preference for macrocyclic contrast agents (gadoteric acid, gadobutrol and gadoteridol) rather than linear contrast agents (including gadobenate dimeglumine [Multihance] and disodium gadoxetate [Primovist]) due to the potential for small amounts of gadolinium to be retained in the globus pallidus and dentate nucleus (https://www.tga.gov.au/alert/gadolinium-based-contrast-agents-mri-scans).

ESC noted that radiologists with MRI accreditation have sufficient expertise in conducting MRI for the populations in this application. ESC considered the possibility of cost-shift towards MBS funds if proposed items are listed.

ESC Key ISSUES	ESC ADVICE
mCRC Clinical Management Algorithm	Query the appropriateness of mCRC algorithm (does not appear to have influenced economic model)
Proposed item descriptor	Consider separate descriptors for mCRC and HCC populations
Proposed Fees	Provide justification for proposed fee for clinical service (to include early + delayed imaging) Provide justification for proposed fee for contrast agent - use of hepatobiliary *vs*. nonspecific (extracellular) contrast (mCRC)

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

The applicant raised concerns about the proposed MBS item being so specific regarding the class of contrast agent to be administered. The applicant stated that while hepatocyte specific agents are very good, times exist when standard contrast agents are superior.

The department raised this concern with the MSAC Executive at its 1 June 2018 meeting. The MSAC Executive agreed that separate liver MRI scan and contrast agent items should be listed to support best clinical practice.

17. Further information on MSAC

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