Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1393 – Cardiac MRI – Cardiomyopathy (Part A)

Applicant: **The Cardiac Society of Australia and New Zealand**

Date of MSAC consideration: **MSAC 67th Meeting, 28-29 July 2016**

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

1. Purpose of application and links to other applications

An application requesting a new Medicare Benefit Schedule (MBS) listing of cardiac magnetic resonance imaging (CMR) for cardiomyopathy was received by the Department of Health from the Cardiac Society of Australia and New Zealand (CSANZ).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness, MSAC did not support the use of CMR in patients with suspected dilated cardiomyopathies (DCMs) due to a lack of evidence and high uncertainty around the clinical effectiveness and cost effectiveness.

MSAC noted CMR may provide value in people with symptoms of heart failure and an inconclusive echocardiogram (Population 1) and in people with symptoms of heart failure in whom echocardiography suggests a non-ischaemic DCM and who have a low risk of coronary artery disease (Population 2a) as there is the potential for CMR to change patient management by providing tissue characterisation, information on aetiology and better estimation of the left ventricular ejection fraction (LVEF) and therefore more accurate determination of the need for implantable devices. MSAC suggested that the value of CMR in these populations could be further explored.

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

MSAC noted that this application (Application 1393 Cardiac MRI Cardiomyopathy – Part A) only examined evidence related to the use of CMR in the investigation of DCMs. MSAC noted that the second part of the application, which investigates the evidence for other types of cardiomyopathies, would be considered at a later date. MSAC also noted that a separate application to use CMR for myocardial stress perfusion and viability imaging in patients with suspected or known coronary artery disease (Application 1237) was also under consideration by the Committee.

MSAC noted that cardiomyopathies are diseases of the heart muscle (myocardium) that are not caused by coronary artery disease (CAD), hypertension, valvular disease or congenital heart disease. DCMs are the most common type of cardiomyopathy and are characterised by dilated ventricles and a reduction in the myocardium's ability to contract or relax. It was also noted that the causes of DCMs are often unknown (idiopathic DCM) but they can be familial, or can be caused by infections, autoimmune disorders, other inflammatory disorders (e.g. sarcoidosis), alcohol, medications or other toxins. While the prevalence and incidence of DCM in Australia is uncertain, it has been estimated that around 1,300 Australians are diagnosed with the condition each year.

MSAC noted that magnetic resonance imaging is a non-invasive imaging technique used to visualise soft tissues. MSAC also noted that the applicant proposed that CMR would diagnose DCMs and could also identify their aetiology (e.g., whether ischaemic or non-ischaemic) through tissue characterisation with and without late gadolinium enhancement (LGE-CMR).

MSAC noted that four separate populations who may benefit from CMR were proposed in the current application. No evidence on the use of CMR was identified in two of these populations and, as a consequence, MSAC dismissed the use of CMR in these patients without further consideration. These populations were:

- asymptomatic first-degree relatives of someone with a diagnosed non-ischaemic DCM, and in whom echocardiography is inconclusive (Population 3); and
- asymptomatic first-degree relatives of someone with a diagnosed non-ischaemic DCM, with an intermediate to high risk of CAD, and in whom echocardiography is suggestive of DCM that requires further investigation before treatment (Population 4).

The remaining two patient populations proposed to benefit from the use of CMR were:

- patients presenting with heart failure symptoms in whom echocardiography is inconclusive (Population 1); and
- patients presenting with heart failure symptoms in whom echocardiography suggests a DCM and who have a low or intermediate risk of CAD (Population 2). This population was further divided into those patients with a low risk of CAD (Population 2a) and those patients with an intermediate risk of CAD (Population 2b).

MSAC noted that there are a number of other invasive and non-invasive imaging tests which could be used as comparators. The non-invasive comparators included gated heart pool scan (GHPS), stress echocardiography (stress-Echo), contrast echocardiography (contrast-Echo), stress single-photon emission computed tomography (SPECT) and computed tomography coronary angiography (CTCA). The invasive comparators were invasive coronary angiography (ICA) and 'further testing' which would largely involve blood tests and, in a small proportion of patients, endomyocardial biopsies.

MSAC accepted that CMR and the other non-invasive imaging tests used as comparators in this application had a good safety profile. MSAC noted that when used during non-invasive testing, contrast agents may cause adverse events in a small number of patients. MSAC noted that CMR did not expose patients to radiation, unlike some of the other non-invasive tests (SPECT, GHPS and CTCA), and was safer than invasive testing modalities such ICA and endomyocardial biopsy.

Population 1

MSAC noted that only one study (Yoshida et al 2013; n = 136) explored the diagnostic accuracy of LGE-CMR in Population 1 (patients presenting with heart failure symptoms in whom echocardiography was inconclusive). The comparator in this study was endomyocardial biopsy and the reference standard was clinical diagnosis based upon all available data. The sensitivity of LGE-CMR was 83% and the specificity was 93%. The study suggested that LGE-CMR would correctly and conclusively confirm the presence of a DCM if it was positive (positive likelihood ratio [LR+] 11.4) and was likely to correctly exclude the presence of a DCM if it was negative (negative likelihood ratio [LR-] 0.18). While these findings suggest that the use of LGE-CMR could influence patient management among people with an inconclusive echocardiogram, MSAC noted that no such evidence was presented.

MSAC accepted the use of contrast-Echo as an appropriate comparator for CMR in Population 1 but noted that contrast-Echo is not MBS-subsidised and is not available in all imaging centres. MSAC noted that the other proposed comparator, GHPS, was rarely used in clinical practice. There was no evidence comparing LGE-CMR with GHPS or contrast-Echo with regards to diagnostic accuracy, change in management or health outcomes. MSAC was unable to reach conclusions about whether LGE-CMR was more accurate, better at characterising tissue as ischaemic or non-ischaemic, or better at changing patient management than the comparators.

MSAC noted that the paucity of evidence presented for Population 1 meant that only a cost comparison analysis was possible. This revealed that LGE-CMR would cost an additional $960 per person compared with contrast-Echo and an additional $688 per person compared with GHPS.

MSAC was unable to support the use of cardiac MRI in Population 1 due to a paucity of supportive evidence and uncertain effectiveness. However, MSAC noted the value of cardiac MRI in correctly diagnosing a DCM or more accurately characterising tissue could not be entirely ruled out.

Population 2 (overall)

MSAC noted that there was lack of evidence comparing the diagnostic accuracy of CMR with non-invasive comparators in Population 2 (patients presenting with heart failure symptoms in whom an echocardiogram suggests a DCM and who have a low or intermediate risk of CAD). One small study (n = 28) compared the accuracy of LGE-CMR and CTCA in categorising a DCM as ischaemic or non-ischaemic using ICA as the reference standard (Hamilton-Craig et al 2012). Both modalities appeared to be highly sensitive and, while LGE-CMR appeared to be less specific than CTCA, this failed to reach significance, possibly due to the small size of the study. No studies comparing the diagnostic accuracy of LGE-CMR to any other non-invasive imaging were identified.

MSAC noted that LGE-CMR appeared to be accurate at distinguishing between non-ischaemic and ischaemic causes of DCM in patients with a dilated left ventricle. When using ICA as the reference standard, the sensitivity of LGE-CMR to detect a non-ischaemic cause ranged between 84–100% and the specificity ranged from 71–100% (Hamilton-Craig et al 2012; Valle-Munoz et al 2009; McCrohon et al 2003; Casolo et al 2006). Similarly when using clinical diagnosis as a reference standard, the sensitivity of LGE-CMR to detect a non-ischaemic cause was 85–100% and specificity was 82–88% (Assomull et al 2011; De Melo et al 2013). Pooling the information from these studies suggested that LGE-CMR would

correctly and conclusively confirm the presence or absence of a non-ischaemic cause of a DCM (LR+ 10.8; LR- 0.09).

MSAC noted that LGE-CMR may be able to diagnose potentially treatable causes of DCM such as inflammation. Three studies compared the ability of LGE-CMR to identify an inflammatory cause of DCM using endomyocardial biopsy as the reference standard (Bohnen et al 2015; Sramko et al 2013; Voight et al 2011). Sensitivity ranged between 58–87% and specificity ranged from 33–50%. However, the specificity of LGE-CMR was higher than endomyocardial biopsy in a separate study when clinical diagnosis was used as the reference standard (93% vs 71%, respectively) suggesting endomyocardial biopsy may be an imperfect reference standard (Yoshida et al 2013).

MSAC noted that LGE-CMR may have some prognostic benefits. Pooling the results of 26 cohort studies in adults revealed that adverse cardiac events were significantly more common in patients with detectable LGE than in those without detectable LGE. MSAC also noted that the application indicated that the presence of detectable LGE may be a stronger predictor of adverse cardiac events than measuring left ventricular ejection fraction (LVEF) and that the measurement of LVEF by echocardiography may be less reliable at predicting cardiac events than measurement of LVEF by CMR. MSAC suggested that further information to tease out this evidence would be helpful in decision making.

Population 2a

MSAC noted that in patients with a low risk of CAD, CMR would be added to other testing to detect treatable causes of non-ischaemic DCM and to provide information on the severity of the condition.

MSAC noted that LGE-CMR can change management in patients already diagnosed as having a non-ischaemic DCM. A single Australian study assessed the impact of LGE-CMR on decisions to undergo surgery or cardiac device implantation in 449 patients with a diagnosed non-ischaemic cardiomyopathy — 90% of whom were estimated to have a DCM (Taylor et al 2013 and personal communication). Documented treatment decisions based upon the findings of investigations undertaken prior to CMR were compared with the decisions made once the additional information from LGE-CMR was known. Use of LGE-CMR led to a change in treatment in 61 (13.6%) patients. Twenty patients received a cardiac device despite there being no original plan for implantation while 21 patients in whom device implantation was planned avoided having a cardiac device implanted. Thirteen of 20 patients scheduled for surgery were able to avoid surgery following CMR, while seven patients underwent surgery despite no original plan to do so. Changes were primarily attributed to LGE-CMR providing a more precise measure of LVEF, which was either above 35% (allowing avoidance of a device) or below 35% (indicating the need for device implantation).

MSAC noted that LGE-CMR was able to identify the cause of a DCM in a small number of people who would have otherwise been classified as having idiopathic DCM. CMR changed the diagnosis in four of 102 patients previously diagnosed as having an idiopathic DCM after standard work-up which included routine blood tests, echocardiography and ICA (Broch et al 2015).

MSAC considered the cost-effectiveness analysis provided for Population 2a despite the considerable uncertainties inherent in the model due to the limited supporting clinical evidence. When the model assumed that LGE-CMR was 100% accurate and led to more appropriate management, the cost of LGE-CMR was an additional $3,158 per patient appropriately managed. MSAC noted that the use of CMR was potentially cost effective until

the accuracy of the test fell below 88%. The model suggested that in Population 2a, every $100,000 spent over a six-month period would lead to 358 LGE-CMRs, 16 additional appropriate devices being implanted and six additional appropriate surgeries. In addition, 17 inappropriate device implantations and nine inappropriate surgeries would be avoided.

MSAC noted that information on the impact of CMR in this population beyond the six-month period would help inform decision making. MSAC suggested that information on the downstream impacts and costs of appropriate or inappropriate device implantation and surgery also be incorporated into the model.

MSAC was unable to support the use of cardiac MRI in Population 2a due to gaps in the clinical evidence, uncertain effectiveness and highly uncertain cost effectiveness. However, MSAC noted that CMR in this population may assist in determining the aetiology of the DCM and may offer advantages in the measurement of LVEF and that this could lead to changes in patient management. MSAC suggested that the value of CMR in this population could be further explored.

Population 2b

MSAC noted that in patients presenting with heart failure symptoms, an inconclusive echocardiogram and an intermediate risk of CAD, CMR would replace other non-invasive tests (CTCA, SPECT or stress-Echo). MSAC noted that no conclusive evidence to support the diagnostic accuracy and effectiveness of CMR compared to these non-invasive imaging modalities was identified. MSAC noted that the incremental cost of CMR was $388 compared with SPECT, $231 compared with CTCA and $504 compared with stress-Echo.

There was a suggestion in the application that LGE-CMR could prevent the need for ICA in some patients (Assomull et al 2011) but there was no strong evidence for this. While a limited cost-effectiveness analysis suggested that use of LGE-CMR to triage patients for ICA was less costly than immediate ICA, MSAC was unable to accept this given the considerable uncertainties in the limited clinical evidence base for this population.

MSAC was unable to support the use of cardiac MRI in Population 2b due to gaps in the clinical evidence, uncertain effectiveness and uncertain cost-effectiveness.

Overall, MSAC was unable to support the use of CMR in all four populations due to a lack of evidence and high uncertainty around clinical effectiveness and cost effectiveness. However, MSAC noted that in Population 1 (people with symptoms of heart failure and an inconclusive echocardiogram), CMR may provide value by ruling a DCM in or out. Similarly, MSAC noted that in Population 2a (people with symptoms of heart failure in whom echocardiography suggests a DCM and who have a low risk of CAD), CMR may be able to provide additional information on aetiology. MSAC also noted that CMR may offer value if it can more accurately assess LVEF and better characterise tissue in these populations.

MSAC agreed that any resubmission for Population 1 would need to use contrast-Echo as a comparator. MSAC noted that the following information would assist it in making a decision about the use of CMR in Population 1:

- the number of Australian centres which are able to conduct contrast-Echo
- the number of transthoracic echocardiograms (TTEs) and the number of contrast-Echos undertaken each year and the proportion of those that are inconclusive. MSAC accepted that this information was unlikely to be publicly available but suggested it could be readily collected from larger imaging centres. MSAC also noted that

information from *Application 1129: Second-generation contrast agents for use in patients with suboptimal echocardiograms* which was previously considered by MSAC could be informative.
- information on the diagnostic accuracy of contrast-Echo and LGE-CMR, including information on the ability of each modality to provide additional information that can inform or change management
- comparative information on the ability of LGE-CMR, standard echocardiography and contrast-Echo to measure left ventricular function accurately and reproducibly
- health outcome information on the appropriate and inappropriate management of these patients (e.g., non-implantation of devices when they should have been implanted and vice versa) and the downstream costs of inappropriate management
- out-of-pocket costs for patients for undergoing contrast-Echo
- presentation of economic data using QALYs, or if this is not possible, health outcomes such as cost of operations avoided, or life years gained, to inform the Committee. This would need to be provided over a longer time horizon rather than the six months currently presented in the model.

MSAC noted that the following information would assist it in making a decision about the use of cardiac MRI in Population 2a:

- clarification of the clinical pathway that leads to the use of LGE-CMR in this population and whether it is expected to replace or be additional to other non-invasive imaging
- information on which patients would be considered to be at low risk of CAD
- an estimate of the number and/or proportion of patients expected to be at low risk of CAD
- the ability of LGE-CMR to identify a cause for the DCM in this population
- information on the ability of LGE-CMR to measure LVEF accurately and reproducibly
- health outcome information on the appropriate and inappropriate management of these patients (e.g., non-implantation of devices when they should have been implanted and vice versa) and the downstream costs of inappropriate management.

MSAC suggested the Department discuss with the applicant a way forward for gathering evidence for these two populations.

4. Background

MSAC has not previously considered Cardiac MRI – Cardiomyopathy (Part A).

5. Prerequisites to implementation of any funding advice

Therapeutic Goods Administration (TGA) status:

There are several MRI devices included on the Australian Register of Therapeutic Goods (ARTG). For the purposes of ARTG classification, MRI machines are considered active medical devices for diagnosis. The classification of devices in this category varies according to the intended purpose of the device. MRI machines are Class IIa (low-medium risk) or Class IIb (medium-high risk) medical devices.

Qualification necessary to perform the proposed medical service:

It is the intention of the applicant that both radiologists and cardiologists trained in CMR will be able to perform CMR services. The level of specialist accreditation recommended by the applicant for performing CMR is equivalent to at least the Society for Cardiovascular Magnetic Resonance (SCMR) level 2 training. The requirement for a minimum level of training for specialists eligible to provide CMR services is encouraged by the Department; however, this will have an impact on the initial availability of CMR services as it is presumed that few Australian radiologists or cardiologists have attained these qualifications to date.

The Royal Australian and New Zealand College of Radiologists and the Cardiac Society of Australia and New Zealand are working together to develop the training requirements for specialists supervising and reporting CMR.

6. Proposal for public funding

The proposed MBS item descriptor is summarised in Table 1.

Table 1 Proposed MBS item descriptor for the investigation of suspected dilated cardiomyopath

Category 5 – Diagnostic Imaging Services **Group I5 – Magnetic Resonance Imaging**
MBS [item number (Note: this will be assigned by the Department if listed on the MBS)] NOTE: Benefits are payable for each service included by Subgroup ## on one occasion only in any 12-month period MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where the request for the scan specifically identifies the clinical indication for the scan - scan of cardiovascular system for: (a) assessment of myocardial structure and function, including tissue characterisation; and (b) the request for the scan identifies that the patient presents with: i. heart failure symptoms, in whom echocardiography is inconclusive or suggests a dilated cardiomyopathy, and in whom further diagnostic clarification is required; or ii. a family history of non-ischaemic dilated cardiomyopathy in a first-degree relative in whom echocardiography is inconclusive. (Contrast) Fee: $855.20Benefit: 75% = $641.40 85% = $726.90

7. Summary of Public Consultation Feedback/Consumer Issues

The Protocol Advisory Sub-Committee (PASC) received two responses from peak bodies, two responses from organisations and one response from a specialist.

Consultation feedback for the protocol was positive. Issues raised in the responses were:

- Current procedure image acquisition time is 60-80 minutes instead of the proposed 45-60 minutes.
- Graded MBS Items could be used to account for varying image acquisition time.
- The protocol states that the procedure can be performed using abdominal, body, thoracic or specialised cardiac coils. Concerns were raised about the image quality of specialised cardiac coils compared to body and thoracic coils.

- The protocol states that specialist referral is required for the procedure due to its complexity, specialist understanding of its uses and limitations, and the interpretation of imaging results. The inclusion of General Practitioner referral for the procedure would ease diagnosis of normal heart function or minor abnormalities.
- Patient access to the procedure may be limited due to difficulty in accessing MRI that has Medicare eligibility.

8. Proposed intervention's place in clinical management

Cardiac MRI is a non-invasive imaging technique that utilises radiofrequency signals to image soft tissues.

Cardiac MRI affords the ability to measure, in one examination, multiple aspects of heart and vascular structure and function. These include, but are not limited to, assessment of left and right ventricular function, myocardial viability, ischaemia assessment, scar assessment, tissue characterisation, imaging of the aorta and great vessels, paediatric and adult congenital abnormality imaging, and imaging of the proximal coronary arteries.

During preparation of the contracted assessment, the PASC-ratified clinical management algorithms were amended. This resulted in a slightly different definition of the population (i.e. patients would not be eligible for CMR if they had a high pre-test risk of CAD), clarification that CMR would be used in family members who are found to have DCM after echocardiography, and amendment of the comparators (i.e. 'watchful waiting' was removed and alternative non-invasive imaging modalities were added as comparators).

With use of the current testing methods for DCM, there is a small, but serious, risk that some of the rarer aetiologies of non-ischaemic dilated cardiomyopathies will not be identified and treated appropriately. Cardiac MRI is an additional imaging tool that would be requested when existing diagnostic methods are inconclusive. Cardiac MRI can also inform prognostic decisions to rule out the need for investigation of first-degree relatives if the aetiology identified is something other than idiopathic or familial cardiomyopathy.

During the assessment process clinical experts provided further clarification and additional information that led to the algorithms being amended.

Figure 1: Proposed clinical pathway for the diagnosis of patients with heart failure (HF) symptoms, in whom echocardiography is inconclusive

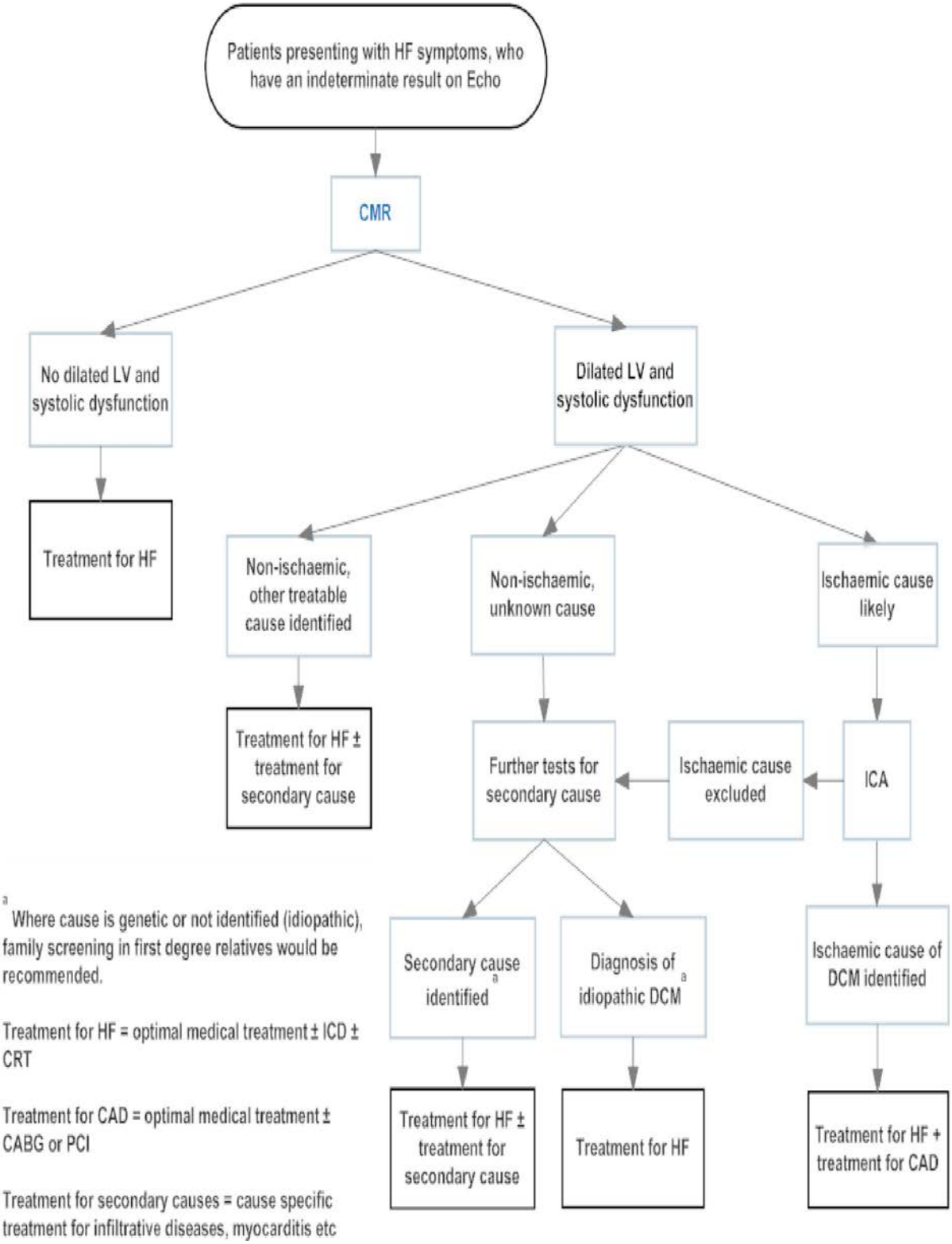
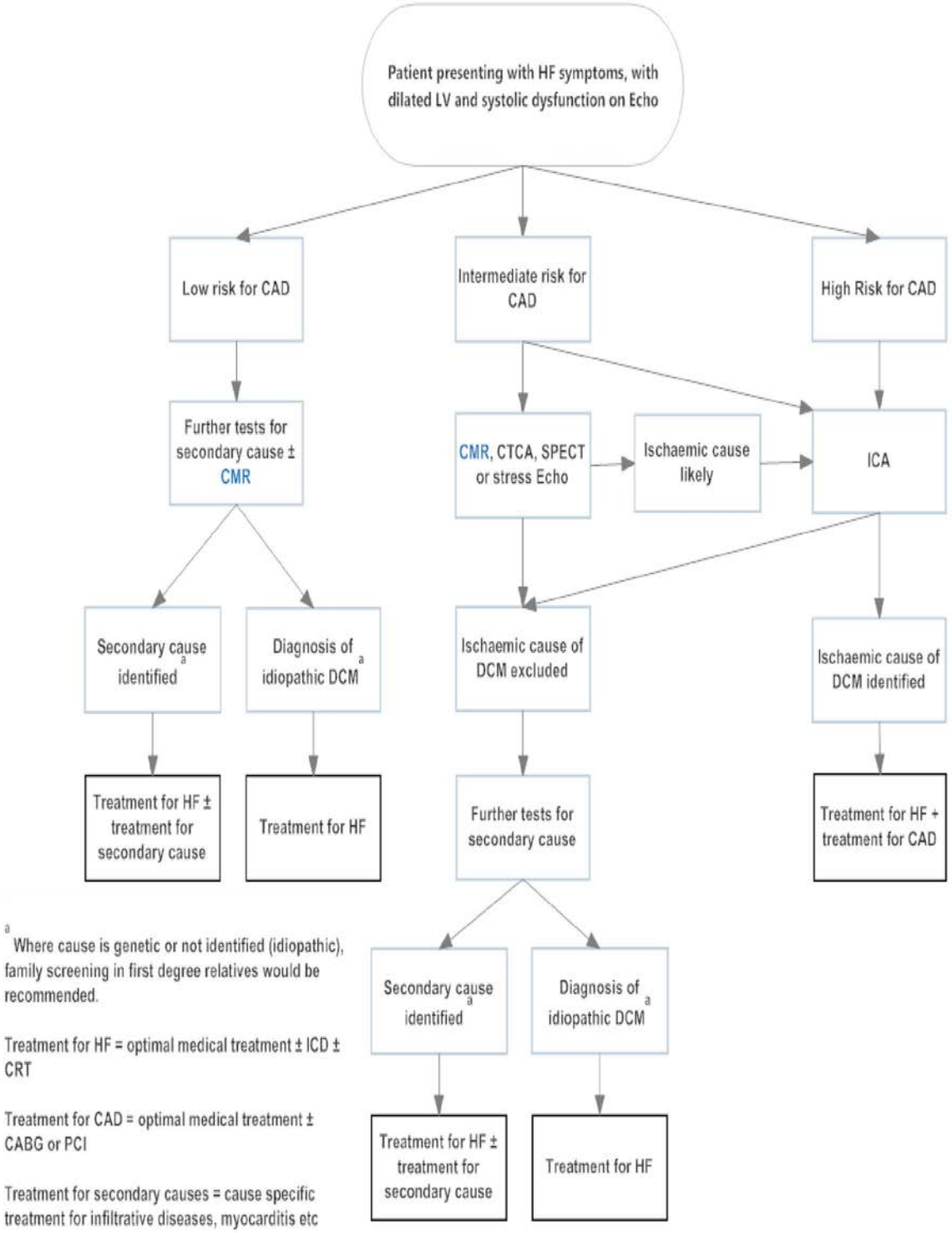


Figure 2: Proposed clinical pathway for the diagnosis of patients with HF symptoms, in whom echocardiography suggests a DCM



9. Comparator

The main comparator is the current practice most likely to be replaced or added to by cardiac MRI. In this case it is those tests used to investigate patients with heart failure symptoms in whom an echocardiography result is unclear or suggests a dilated left ventricle (LV) and systolic dysfunction, and in whom further diagnostic clarification is required.

These tests include:

1. Gated heart pool scan (GHPS) (MBS item 61313)
2. Stress echocardiography (MBS items 55116, 55117, 55122, 55123)
3. Contrast echocardiography
4. Invasive coronary angiography (ICA) (MBS items 38215, 38218)
5. Computed tomography coronary angiography (CTCA) (MBS Items 57360, 57361)
6. Exercise or pharmacologic (adenosine or dobutamine) single-photon emission computed tomography (SPECT) (MBS Items 61302, 61303, 61306, 61307, 61651, 61652, 61653, 61654)
7. Further tests

10. Comparative safety

Test adverse events

The identified systematic review did not report any adverse events (AEs) from the CMR procedure itself or from the comparator tests. All the non-invasive tests are considered to have a good safety profile, although rare AEs may occur as a consequence of the contrast agents and tracers used in LGE-CMR, contrast echocardiography, SPECT, GHPS and CTCA; and the radiation used in SPECT, GHPS and CTCA. The invasive testing modalities, such as ICA and endomyocardial biopsy (EMB), have higher rates of complications than the non-invasive imaging techniques. EMBs involve sampling of heart tissue; and ICA involves contrast, radiation and catheterisation through patient's arteries.

AEs from change in management

Evidence from one Australian study suggests that the use of CMR will provide clinicians with more information on which to base treatment decisions, and allow patients to be appropriately treated more conservatively (i.e. fewer patients are likely to have cardiac devices implanted or undergo surgery). This would have corresponding safety benefits.

11. Comparative effectiveness

The accuracy of CMR was considered using three different concepts. It was proposed as a means to diagnose DCM, distinguish between ischaemic and non-ischaemic DCM, and determine the aetiology of non-ischaemic DCM (NIDCM) in those diagnosed with idiopathic DCM. CMR was also proposed to predict health outcomes and influence patient management. Overall, it is clear that CMR provides information that is useful for determining a patient's prognosis, and could potentially be helpful at deciding which treatments patients should receive.

There is no direct evidence available to demonstrate that CMR benefits the health of patients, but a linked evidence approach suggests that it is likely. A brief summary of findings is shown in Table 2.

Table 2 Summary of findings for the linked evidence comparison of CMR for DCM

Section in report	Outcomes	Participants (studies)	Results	Interpretation	Quality of evidence using GRADE
B2. Direct evidence	Safety of CMR and comparative tests	K=0	No studies were identified on the harms of CMR or comparative imaging techniques for the population with DCM.	The non-invasive imaging techniques have good safety profiles. Invasive testing such as EMB and ICA has higher rates of complications.	N/A
B3. Diagnostic performance	Accuracy of CMR for diagnosing DCM	N=136 K=1 diagnostic accuracy study	Sensitivity = 0.83 (0.71, 0.92) Specificity = 0.93 (0.85, 0.97)	CMR is reasonably good at identifying DCM, when compared with clinical diagnosis and EMB. However, these findings were in studies that included patients other than those with an inconclusive echocardiogram.	Moderate ⊕⊕⊕⊙
	Accuracy of CMR at distinguishing ICM from NIDCM	K=8 diagnostic accuracy studies (K=6 vs ICA, K=2 vs clinical diagnosis)	Sensitivity = 0.68–1.00 Specificity = 0.71–1.00	A high proportion of those patients with NIDCM may avoid ICD insertion if imaged with CMR.	Low ⊕⊕⊙⊙ to High ⊕⊕⊕⊕
B3. Diagnostic performance; B4.2. Prognosis or predisposition	Accuracy of CMR vs CTCA, SPECT, or stress echo or contrast echo	K=1 diagnostic accuracy study; 2 prognostic studies	Only very limited evidence compared with CTCA Contradictory evidence compared with SPECT No evidence compared with stress or contrast echocardiography.	Conclusions on the comparative accuracy or prognostic benefit of CMR vs alternative non-imaging techniques cannot be made.	Very low ⊕⊙⊙⊙
B5.1. Therapeutic efficacy	Diagnostic yield of CMR in those classified as having idiopathic DCM	N=102 K=1 comparative diagnostic yield study	CMR identified aetiologies in 4/102 patients. 3/4 aetiologies were not identified by any other further test. 1/4 patients were also identified by EMB.	CMR provides unique information, identifying a small number of cases who would otherwise be classified as having idiopathic NIDCM. None of the other tests could be replaced by CMR, as each reported unique aetiologies.	Very low ⊕⊙⊙⊙
B4.2.	LGE-CMR	K=30	All-cause mortality RR	Those with signs of	Low

Section in report	Outcomes	Participants (studies)	Results	Interpretation	Quality of evidence using GRADE
Prognosis or predisposition	for determining prognosis in those with NIDCM	prospective or retrospective cohort studies	= 2.47 (95%CI 1.63, 3.74) Cardiac deaths RR = 3.21 (95%CI 1.79, 5.76) Any cardiac event RR = 3.71 (95%CI 2.29, 6.04)	scarring or inflammation on LGE-CMR had worse cardiac outcomes than those without signs, and were more likely to have an ICD implanted and to have an appropriate ICD shock.	⊕⊕⊙⊙ to Moderate ⊕⊕⊕⊙
B5.1. Therapeutic efficacy	Effect of CMR on device implantation and surgery for NIDCM	N=488 K=1 cohort study	In those patients scheduled for devices, 21/72 (29.2%) avoided implantation following CMR imaging. In those not scheduled for devices, 20/375 (5.3%) had one implanted after CMR imaging. In those scheduled for surgery, 13/20 (65%) avoided surgery after CMR. In those not scheduled for surgery, 7/427 (1.6%) underwent surgery after CMR.	CMR is effective at reducing the proportion of patients who receive devices or surgery for treatment of CM, compared with what is done currently in Australia. Only a small proportion of patients who would otherwise not receive devices or surgery had their treatment plan amended following investigation with CMR. Appropriate avoidance of invasive therapies would result in superior safety outcomes.	Moderate ⊕⊕⊕⊙
B5.2. Therapeutic effectiveness	Effectiveness of corticosteroids for myocarditis	N=719 K=8 RCTs	Mean LVEF difference = 7.36% (95%CI 4.94, 9.79), favouring corticosteroids over no corticosteroids after 1–3 months No significant difference in mortality	Treatment specific for myocarditis may improve cardiovascular functioning, compared with general treatment for HF symptoms.	Moderate ⊕⊕⊕⊙
	Effectiveness of revascular-isation for ICM	N=93,553 K=100 RCTs	CABG reduces the risk of death, myocardial infarction and subsequent revascularisation, compared with medical treatment alone. There were no data specific to patients who were negative for scarring or	Correct identification of ICM is likely to reduce patient cardiac deaths and other outcomes. However, the impact of an incorrect diagnosis of NIDCM in those who are LGE– is unknown.	Low ⊕⊕⊙⊙

Section in report	Outcomes	Participants (studies)	Results	Interpretation	Quality of evidence using GRADE
			inflammation using LGE-CMR.		

CABG = coronary artery bypass grafting; CI = confidence interval; CM = cardiomyopathy; CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; CTCA = computed tomography coronary angiography; Echo = echocardiography; EMB = endomyocardial biopsy; HF = heart failure; ICA = invasive coronary angiography; ICD = implantable cardioverter defibrillator; ICM = ischaemic cardiomyopathy; K = number of studies; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance (imaging); LVEF = left ventricular ejection fraction; N = number of patients; NIDCM = non-ischaemic dilated cardiomyopathy; RCT = randomised controlled trial; RR = relative risk; SPECT = single-photon emission computed tomography

In patients having a CMR after an indeterminate result from echocardiography (Population 1), CMR is safe but of uncertain effectiveness.

Based on a linked evidence approach (summarised above), in patients with a low risk of CAD (Population 2a), the addition of CMR to further blood tests is safe and effective for determining the aetiology of NIDCM. This benefits a small number of patients with rare DCM aetiologies, and rules out the need for familial screening in these cases. CMR also has the capacity to accurately target a significant number of patients to different treatments than would have been received on the basis of current tests alone; however, the impact of these changes in management on patient health are uncertain.

In patients with an intermediate risk of CAD (Population 2b), CMR has uncertain effectiveness compared with CTCA, SPECT and stress echocardiography for determining ischaemia. It is effective at triaging NIDCM patients away from ICA. This population is, in part, considered under Application 1237.

12. Economic evaluation

The limited and fragmented nature of the clinical evidence did not enable construction of a single economic model to generate an overall cost-effectiveness estimate for the proposed MBS listing. Rather, individual economic analyses for each of the various patient subpopulations and between the relevant comparators were performed, to the extent that available data allowed.

In Population 1: patients with inconclusive echocardiogram results—a **cost comparison analysis of CMR vs contrast echocardiography or GHPS**.

- Including costs associated with the testing procedure, and with AEs associated with the testing and test follow-up, the additional cost of CMR over GHPS is approximately $688 per person, and over contrast echocardiography approximately $960 per person.
- CMR remained more expensive than either of these comparators in all sensitivity analyses.

In Population 2: patients diagnosed with DCM on echocardiogram and requiring further diagnostic clarification, the population was further divided into two subgroups:

- Subpopulation 2a: patients with a low risk of CAD (or where CAD has been ruled out - a (limited) **cost-effectiveness analysis of CMR as an additional diagnostic test**

  Assuming that addition of CMR (vs no CMR) was 100% accurate and provided for more-appropriate management, the base-case results of the analysis suggest that, after 6 months, CMR would cost an additional $3,158 per additional patient appropriately managed (or inappropriate management avoided).

  It is assumed that CMR is 100% accurate in the base-case, but if the sensitivity of CMR is less than 88% relative to the alternative of 'all diagnostic reference data', then the use of CMR would become less effective and more costly than not using it.

- Subpopulation 2b: patients with an intermediate risk of CAD, where the next investigation is to rule out CAD - a (limited) **cost-effectiveness analysis of CMR vs ICA**, and a **cost comparison analysis of CMR vs SPECT, CTCA or stress echocardiography.**

  Cost-effectiveness analysis: The base-case model found that use of CMR to triage patients for ICA was both more effective (in terms of avoiding unnecessary ICAs) and less costly (i.e. dominant) than immediate ICA, primarily because of the high relative cost of ICA, and the choice of outcome (i.e. simply reflecting a preference to avoid invasive testing, rather than overall health outcomes).

  Although inputs were uncertain, this conclusion held across all plausible sensitivity analyses conducted.

  Cost comparison analysis: CMR testing is associated with an incremental cost of $388 compared with SPECT, $230 compared with CTCA, and $504 compared with stress echocardiography.

  It remained more costly in all sensitivity analyses.

No reliable economic analyses were possible for Subpopulations 3 and 4, described in the listing as encompassing asymptomatic family members of patients with NIDCM.

Overall, given the large gaps in comparative clinical outcome data and the identification of incremental cost estimates in opposite directions across different patient groups, it is not possible to form a generalised conclusion of the cost-effectiveness of CMR as per the proposed listing. Rather, only limited conclusions can be drawn for the specific patient groups and circumstances.

The total cost associated with each use of CMR in the economic analysis is $1,106, which includes the cost of the listing, $855.20 (including patient co-payments), the cost of referrals for testing (where applicable) and the cost for treating AEs related to the testing methodology.

13. Financial/budgetary impacts

Estimations of the extent of use and financial implications of CMR are highly uncertain. A combination of epidemiological and market share approaches, with numerous assumptions, were required to estimate the financial impact. Based on a reported incidence rate for

primary DCM, the ratio of ischaemic to non-ischaemic causes of DCM, estimated rates of eligible family members per index case and uptake rates, the following estimates of CMR usage and its directly associated costs were projected (Table 3).

Table 3: Number of CMR tests for suspected DCM (by subpopulation) and total costs

	2016–17	2017–18	2018–19	2019–20	2020–21
Population 1: expected uptake	640	651	662	672	683
Population 2: expected uptake	3,338	3,395	3,451	3,507	3,562
Populations 3 and 4: expected uptake	108	109	111	113	115
Total projected number of CMR tests for DCM	**4,086**	**4,155**	**4,224**	**4,292**	**4,360**
Cost of CMR and associated items to the MBS [a]	$3,125,411	$3,178,692	$3,231,539	$3,283,585	$3,335,423
Cost of CMR and associated items to patients [b]	$299,310	$304,412	$309,473	$314,458	$319,422
Total cost of CMR	**$3,424,721**	**$3,483,104**	**$3,541,012**	**$3,598,043**	**$3,654,845**

[a] $765 per service, [b] $73.26 per service
CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; MBS = Medicare Benefits Schedule
Population 1: symptomatic patients with indeterminate echocardiogram results; population 2: patients requiring further diagnostic clarification of DCM; populations 3 and 4: familial cases eligible for CMR

Calculation of cost offsets is complex given the range of comparators across the different populations for this assessment of CMR. Overall, some cost offset is assumed for approximately 84% of CMRs (i.e. CMR is anticipated to replace an alternative test), based on assumptions around existing and anticipated clinical management within the population subgroups and estimated test uptake rates within the populations. The offsets are apportioned across: GHPS (15%), contrast echocardiography (3.8%), ICA (43%), CTCA (28%), stress echocardiography (5.5%) and SPECT (4.1%), based on existing market share estimates. The estimated net impact on the MBS budget is presented in Table 4.

Table 4 Total costs to the MBS associated with CMR for suspected DCM

	2016–17	2017–18	2018–19	2019–20	2020–21
Number of proposed CMR services	4,086	4,155	4,224	4,292	4,360
CMR cost to the MBS	$3,125,411	$3,178,692	$3,231,539	$3,283,585	$3,335,423
Number of services offset	3,413	3,472	3,529	3,586	3,643
Costs offset	$1,573,853	$1,600,683	$1,627,295	$1,653,504	$1,679,608
Net cost to the MBS	$1,551,558	$1,578,008	$1,604,243	$1,630,081	$1,655,815

CMR = cardiac magnetic resonance (imaging); DCM = dilated cardiomyopathy; MBS = Medicare Benefits Schedule

The estimates of net cost are highly uncertain. They are directly sensitive to any changes in the estimates of the incidence of DCM, and the assumptions associated with estimating cost offsets.

14. Key issues from ESC for MSAC

There are 4 populations included in the application. However, there is no evidence for proposed Populations 3 and 4. ESC also advised that Population 2 be split into 2(a) low risk of coronary artery disease (CAD) and (b) intermediate risk of coronary artery disease (CAD).

The populations are:

1. People presenting with heart failure symptoms, in whom echocardiography (Echo) is inconclusive;
2. People presenting with heart failure symptoms, in whom Echo suggest dilated cardiomyopathy, and have low or intermediate risk of coronary artery disease;
3. Asymptomatic first degree relatives of someone diagnosed with non-ischaemic dilated cardiomyopathy, in whom Echo is inconclusive (no evidence)
4. Asymptomatic first degree relatives of someone diagnosed with non-ischaemic dilated cardiomyopathy, in whom Echo suggests a dilated cardiomyopathy, which requires further investigation prior to treatment, due to an intermediate – high risk of coronary artery disease.

Population 1

For Population 1, clinical utility for cardiac MRI for this indication lies with the fact that the usual test (Echo) is inconclusive and current comparators are either not highly utilised (GHPS) or not MBS listed (contrast-Echo), and assessment of left ventricular ejection fraction (LVEF) is of clinical benefit.

Population 2

For Population 2, where there is low to intermediate risk of CAD as the cause for DCM, the clinical utility lies in the detection of less common aetiologies e.g. myocarditis rather than CAD – these are smaller subsets of the DCM population.

Safety

For Populations 1 and 2, there are no issues with safety. However, the clinical evidence is fragmented and of low quality and has no direct evidence to demonstrate patient health benefits. The linked evidence is sub-optimal in many cases and varied across the populations included in the application.

Examples are:

- For Population 1: cardiac MRI is safe but of uncertain effectiveness
- For Population 2a (low risk of CAD): addition of cardiac MRI is safe and effective for determining the aetiology of NIDCM
- For Population 2b (intermediate risk of CAD); cardiac MRI has uncertain effectiveness compared to other tests – but appears effective at triaging NIDCM patients away from ICA.
- For Populations 3 and 4 – the effectiveness is uncertain as there is no evidence

ESC also advised that the economic evaluation has inadequacies in the data which limit the ability to perform an economic analysis. No economic analysis could be undertaken for Populations 3 or 4.

ESC advised that it agreed with the policy issues, which include:

- Supervision - Currently MRI can be performed by anyone who is under the professional supervision of an eligible provider who is available to monitor and influence the conduct and diagnostic quality of the examination, including, if necessary, by personal attendance on the patient. Radiologists are not required to be at the practice location during the performance of the scan as there is no clear definition of when it is 'necessary' for them to attend the patient. The applicant has indicated that it is the intention to require the providing specialist to personally attend the patient during the examination. The policy area would include this in the item descriptor.
- Performance of the MRI can be managed via the item descriptor. The person who operates the MRI equipment, prepares the patient for the scan, administers the contrast agent and captures the image is not required to have any qualifications, provided they are under the supervision of a radiologist as described above. The policy area recommends that registered medical radiation practitioners be specified to undertake cardiac MRI under the supervision of a specialist trained in CMR. This could be managed through the item descriptor.
- CMR reporting – Inclusion of cardiologists will require legislative changes to the Diagnostic Imaging Services Table (DIST) regulations. It is the intention of the applicant that radiologists and cardiologists trained in cardiac MRI will be able to report cardiac MRI services. Current legislative requirements stipulate that Medicare eligible MRI items must be reported on by a specialist in diagnostic radiology who satisfies the Chief Executive Medicare that the specialist is a participant in the Royal Australian and New Zealand College of Radiologists' (RANZCR's) Quality and Accreditation Program (*Health Insurance (Diagnostic Imaging Services Table) Regulations – 2.5.4 – Eligible Providers*).
- Accreditation under the Diagnostic Imaging Accreditation Scheme (DIAS) may limit the number of cardiologists able to provide cardiac MRI services that are eligible for MBS reimbursement. The inclusion of cardiologists will require formal legislative changes to the *Health Insurance (Diagnostic Imaging Services Table) Regulations.*
- All sites providing CMR will need to have Medicare eligibility (either full or partial); be considered a comprehensive practice (which requires a practice to provide x-ray, ultrasound, CT and MRI services at the one location); and be accredited under the DIAS. The requirement for a practice to be considered comprehensive may impact the number of cardiologists able to provide CMR services.

<u>Effectiveness</u>

ESC advised in relation to effectiveness that:

- Population 1 was uncertain
- Population 2a (low CAD risk) – effective (in rare DCM aetiologies and potentially rules out need for familial screening)
- Population 2b (intermediate CAD risk) – uncertain but may be effective at triaging away from ICA, and
- Populations 3 and 4 have no evidence pertaining to effectiveness.

Clinical claim

ESC advised that there are 12 diagnostic accuracy studies, although they are generally low quality and the prognostic cohort studies are similar. Cardiac MRI may be more accurate than Echo for assessing LVEF (tends to be higher with cardiac MRI), which is used to determine whether patients should receive an ICD.

- Population 1; cardiac MRI substitutes
- Population 2; cardiac MRI partially replaces some comparators or is an additional test

ESC are uncertain if cardiac MRI gives a higher or lower left ventricular ejection fraction (LVEF) than Echo, they believe that there can be misclassification in both directions.

Economic analysis

ESC advised that the economic analysis was difficult.

- Population 1 – cost comparison
- Population 2a (low CAD risk) – limited cost effectiveness analysis (CEA) as an additional test
- Population 2b (intermediate CAD risk) – limited cost effectiveness analysis of CMR vs ICA and cost comparison for cardiac MRI vs SPECT, Echo or CTCA

No economic analysis could be undertaken for Populations 3 or 4.

Cardiac MRI

T1, T2 and T2* relaxation times and LGE may provide differentiation between CAD, DCM and myocarditis.

ESC advised that there are some key inputs apart from safety and effectiveness. These include: large gaps in clinical outcome data; that numerous assumptions are uncertain; and the cost calculations were difficult. While policy issues were also identified, these could be managed, should the application proceed.

15. Other significant factors

Nil.

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

The applicant had no comment.

17. Further information on MSAC

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