Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1713 – Cardiac MRI in the diagnosis of myocarditis

Applicant: **Cardiac Society of Australia and New Zealand (CSANZ)**

Date of MSAC consideration: **4-5 April 2024**

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 cardiac magnetic resonance imaging (MRI) for the diagnosis of myocarditis was received from the Cardiac Society of Australia and New Zealand (CSANZ) by the Department of Health and Aged Care.

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 MBS item for cardiac MRI for the diagnosis of myocarditis in patients with acute onset (<3 months duration) of heart failure or unexplained arrhythmia suspected due to myocarditis. MSAC considered there was an unmet clinical need for improved diagnosis of myocarditis in these patients. MSAC noted the evidence demonstrated that cardiac MRI has high sensitivity and specificity in diagnosing myocarditis compared to the 'reference standard' endomyocardial biopsy (EMB) test, and also has superior safety. Despite the lack of direct evidence for change in management and improvement in health outcomes, MSAC noted cardiac MRI is an established tool, validated for the radiological diagnosis of myocarditis, but does not diagnose the underlying cause of myocarditis. MSAC noted that cardiac MRI is widely recommended for this purpose in international clinical practice guidelines. MSAC considered publicly funding this testing would improve equity of access for patients who would otherwise require diagnosis using the invasive EMB procedure. MSAC considered that the proposed fee was high, as it was not aligned with comparable MBS items. Although the cost-effectiveness and total financial impact of the service were relatively uncertain, MSAC considered the net financial impact on the MBS to be modest. MSAC noted that cardiac MRI for this population was proposed to replace the current temporary MBS item (63399) that was listed to aid in diagnosing myocarditis associated with mRNA COVID-19 vaccination and scheduled to cease in December 2024, the majority of whom would be covered under the supported item above. MSAC noted that in not supporting the proposed item for the population with acute coronary syndrome (ACS), it may result in a service gap for some patients currently able to access this service under MBS Item 63399. In the context of current utilisation of 63399, MSAC considered the proportion of patients with vaccine-related myocarditis who would experience a service gap will be very small. To ensure the supported item is fit for purpose, as part of the implementation process the Department will consult with the sector and will monitor impact post-implementation.

MSAC did not support public funding of cardiac MRI for patients presenting with signs and symptoms of ACS with an intermediate risk of obstructive coronary artery disease (CAD), or suspected myocarditis (other than patients with signs and symptoms of acute onset cardiomyopathy that is suggestive of acute myocarditis, as above). MSAC considered the population to be very broad and risk of unintended use of the service beyond the proposed population to be high with associated increased MBS expenditure. MSAC noted the proposed clinical place of cardiac MRI in the treatment algorithm was not representative of current clinical practice for ACS as these patients would undergo coronary imaging before cardiac MRI testing to rule out obstructive CAD. Consequently, MSAC considered the assumption that computed tomography coronary angiography (CTCA) ± transthoracic echocardiogram (TTE) would be avoided was uncertain and cost-offsets unlikely to be realised. MSAC considered that the cost-effectiveness and total financial impact for this population with ACS was highly uncertain due to lack of local data and likely underestimated due to the assessment not taking into account additional testing that may be occurring through the private health system.

MSAC's supported MBS item descriptor is provided below in Table 1.

Table 1 MSAC's supported MBS item descriptor

Category 5 – DIAGNOSTIC IMAGING SERVICES – Group I5 – Magnetic resonance imaging
MBS item *XXXX Proposed item descriptor: MRI scan of cardiovascular system for the assessment of myocardial structure and function and characterisation, if the service is requested by a specialist or consultant physician who has assessed the patient, and the request for the scan indicates the patient has acute onset (<3 months) of heart failure or unexplained arrhythmia suspected due to myocarditis, and would otherwise require endomyocardial biopsy to confirm the diagnosis. (R) (Anaes.) (Contrast)
Fee: $TBC Benefit: 75% = $TBC 85% = $TBC Plus: GBCA MBS item 63491: Fee: $47.40 Benefit: 75% = $35.55 85% = $40.30

GBCA = gadolinium-based contrast agent; MBS = Medicare Benefits Schedule

Consumer summary
This application from the Cardiac Society of Australia and New Zealand (CSANZ) requested Medicare Benefits Schedule (MBS) listing of cardiac magnetic resonance imaging (MRI) for the diagnosis of myocarditis. Myocarditis is a condition that occurs when the heart muscle (myocardium) becomes inflamed. Inflammation can be caused by an infection, or by a non-infectious cause. Acute myocarditis is the most common type of myocarditis (two thirds of cases) and has a short time between when symptoms start and diagnosis, usually less than one month. Cardiac MRI is a test that uses a magnetic field and radiofrequency waves to create detailed pictures of the heart and arteries. MRI is called a "non-invasive" test because it takes an image without surgery. Diagnosing myocarditis is often hard because it can have many different causes and symptoms. Currently, myocarditis can be diagnosed using a range of tests. This application proposed using cardiac MRI to diagnose acute myocarditis in the following two patient types (populations): • Population 1: Patients with signs and symptoms of acute heart failure and/or arrythmia (acute onset cardiomyopathy) suggestive of acute myocarditis.

Consumer summary

- Population 2: Patients presenting with signs and symptoms of sudden reduced blood flow to the heart (acute coronary syndrome [ACS]) with an intermediate risk of blockage of blood flow to the heart due to narrowing or closing of arteries that supply the heart with blood (obstructive coronary artery disease [CAD]), or suspected myocarditis.

MSAC noted that population 1 patients are currently diagnosed with myocarditis using a number of tests, including an invasive heart muscle biopsy (endomyocardial biopsy [EMB], which takes a small sample of muscle from the heart for testing), but the biopsy may not always identify the underlying cause. Cardiac MRI is an established tool for making a diagnosis of myocarditis and is recommended in international guidelines. Because there was not much relevant evidence, the economic and financial assessments had to rely on expert opinion, which made them uncertain. But MSAC considered that listing the service would improve equity for patients who would otherwise require a heart biopsy to diagnose myocarditis, which is invasive and less safe than MRI. While there was not much evidence that getting a diagnosis would change a patient's treatment and improve their health, on balance MSAC accepted that getting a diagnosis probably will change treatments in line with clinical guidelines. MSAC advised that the value for money and the overall cost to the MBS for this population were acceptable. Therefore, for population 1 MSAC supported cardiac MRI testing to diagnose acute myocarditis.

MSAC noted that the applicant proposed a permanent MBS item for cardiac MRI to replace the current temporary MBS item (63399) that was listed to aid in diagnosing myocarditis associated with mRNA COVID-19 vaccination. The temporary item is scheduled to end in December 2024, and MSAC considered that most of these people will be covered under the new MBS item in the future, which was acceptable given how much the temporary item is being used at the moment.

MSAC considered that the current fees for similar MBS items do not justify the proposed fee, and advised the fee should be lower than the applicant proposed. MSAC requested the department policy area review the fees of MBS items for MRI to make sure the fees are consistent between similar items and reasonable.

For population 2, the applicant stated that patients with a low risk of CAD would no longer need current types of imaging, and would instead have cardiac MRI as the first test. However, MSAC considered that in real-world practice the current tests for CAD would most likely still happen before a cardiac MRI for patients within population 2. This means that cardiac MRI would be an extra test for these patients, rather than replacing current tests. This made the purpose of adding a cardiac MRI unclear, and the value for money and cost to the MBS uncertain, so MSAC did not support use of cardiac MRI for ACS patients with intermediate risk of obstructive CAD.

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

MSAC supported listing the of cardiac MRI in the diagnosis of myocarditis in patients with signs and symptoms of acute onset cardiomyopathy (acute heart failure and/or arrythmia) suggestive of acute myocarditis, because it will allow them to avoid an invasive biopsy. However, MSAC did not support cardiac MRI for other patients where there was insufficient evidence that it would be useful.

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

MSAC noted that this application requesting MBS listing of cardiac magnetic resonance imaging (MRI) for the diagnosis of myocarditis was received from the CSANZ by the Department of Health and Aged Care.

MSAC recalled that in April 2017, it had considered *Application 1432 – Cardiac MRI of patients with suspected non-ischaemic cardiomyopathy (Part B)*[1]. Population 5 of application 1432 included patients with cardiomyopathies due to ACS, myocarditis or Takotsubo cardiomyopathy (TTC). MSAC recalled it had not supported population 5 at the time because the cost-effectiveness was highly uncertain due to limited evidence on long-term health outcomes. MSAC noted that population 5 from application 1432 was similar to population 2 in the current application. MSAC also noted that, the MSAC Executive supported a temporary cardiac MRI MBS item that was introduced on 1 January 2022 for suspected mRNA COVID-19 vaccine-associated myocarditis (MBS item 63399); however, a full health technology assessment (HTA) had not been done for the temporary item. MSAC noted the temporary item was extended on 19 August 2022 and is scheduled to cease on 31 December 2024.

MSAC noted that this application was initiated following discussions between the Department and the applicant in relation to the temporary cardiac MRI item and the need for a HTA.

MSAC noted that myocarditis is inflammation of the heart muscle (myocardium) characterised by presence of inflammatory infiltrate, degenerative and necrotic changes to cardiomyocytes. MSAC noted although the aetiology of myocarditis remains unknown in ~50% of cases, it has a large number of aetiologies including viral infections, drugs, environmental factors and autoimmune diseases. The diagnosis of myocarditis is challenging as patient presentation ranges from being asymptomatic to presenting with subtle cardiac dysfunction through to cardiogenic shock or sudden death. The symptoms can mimic ACS and include a sudden onset of acute chest pain, dyspnoea, persistent or intermittent palpitations within <1 month of symptom onset and diagnosis.

MSAC noted that current tests for diagnosis of myocarditis were non-specific. The reference standard test currently used for diagnosing myocarditis is endomyocardial biopsy (EMB), which is invasive, often challenging to perform and is only performed in certain specialist centres. Therefore, patients are typically diagnosed with clinically suspected myocarditis based on signs and symptoms and through other cardiac tests to exclude other possible heart conditions.

MSAC noted cardiac MRI is a non-invasive test to assess the structure and function of the heart and is comparatively safe due to the absence of ionising radiation. MSAC noted cardiac MRI is an established tool, validated for the radiological diagnosis of myocarditis and is widely recommended for this purpose in international clinical practice guidelines. MSAC noted that cardiac MRI is listed on the MBS for indications such as investigation of congenital heart disease, aortic disease, arrhythmogenic right ventricular cardiomyopathy and cardiac mass.

MSAC noted consultation input from six (6) professional organisations, two (2) consumer organisations and seven (7) individuals, of which 6 were specialists and 1 a family member of a consumer with feedback being supportive for the application.

MSAC noted that in the current application, the use of cardiac MRI in diagnosis of acute myocarditis was proposed for the following two populations:

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[1] MSAC Public Summary Document (PSD) Application 1432, April 2017

- Population 1: Patients with signs and symptoms of acute onset cardiomyopathy (acute heart failure and/or arrythmia) suggestive of acute myocarditis.

- Population 2: Patients presenting with signs and symptoms of ACS with an intermediate risk of obstructive CAD, or suspected myocarditis.

MSAC noted the proposed clinical management algorithms. For population 1 following standard investigations, if patients are haemodynamically stable, they would undergo cardiac MRI. MSAC noted haemodynamically unstable patients would require an EMB procedure for diagnosis and to guide their treatment. MSAC noted that applicant stated 80% patients could avoid an invasive EMB test if cardiac MRI testing was supported. MSAC noted for population 2, myocarditis can mimic ACS in patients with intermediate pre-test risk of CAD. After standard investigations if ACS is suspected, patients that are stable and have an intermediate risk would receive a cardiac MRI. MSAC noted the patients with cardiac MRI findings that are not consistent with myocarditis would then go on to receive a CTCA. MSAC considered population 2 was broad due to the various aetiologies of ACS mimic, making it difficult to characterise, and thus there was a high risk of leakage of cardiac MRI in population 2. MSAC considered population 2 represented 2 sub-populations, one being patients with signs and symptoms of acute coronary syndrome (ACS) with an intermediate risk of obstructive coronary artery disease (CAD), and the other patients with suspected myocarditis without signs and symptoms of acute onset cardiomyopathy. MSAC considered there was limited evidence presented in the application for the latter patients who would require EMB or would benefit from late gadolinium enhancement (LGE) prognostic information.

MSAC noted ESC and department concerns that in real-world practice, cardiac MRI would be done after coronary imaging (i.e., CTCA). MSAC noted in the pre-MSAC response that the applicant stated that CAD did not have to be initially excluded and so cardiac MRI would replace CTCA, referring to the international guidelines and stating cardiac MRI is the first-line investigation for the diagnosis of myocarditis. However, MSAC noted this was inconsistent with the European Society of Cardiology Heart Failure guidelines[2] referenced in the pre-MSAC response that stated diagnostic workup in suspected acute myocarditis is preferred by cardiac MRI in the absence of significant coronary artery, valvular or congenital heart disease, or other causes. Therefore, MSAC agreed with ESC and concluded that the claimed cost-offset due to reduction in CTCA± TTE would likely not be realised in real-world practice.

MSAC noted that the applicant proposed different comparators for the two populations for cardiac MRI:

- The comparator proposed for population 1 was standard management (e.g., anti-failure treatment, circulatory support, antiarrhythmic treatment) for clinically suspected acute myocarditis, with or without EMB when clinically indicated.
- In population 2, the comparator suggested by the applicant was standard management of intermediate-risk ACS, including CTCA/ICA to exclude obstructive CAD ± TTE.

Regarding comparative safety, MSAC agreed with ESC that the claim of superior safety of cardiac MRI was likely reasonable due to the fact that cardiac MRI is non-invasive and has a good safety profile without exposure to ionising radiation. MSAC considered publicly funding cardiac MRI would improve equity of access for patients who would otherwise require diagnosis using the invasive EMB procedure.

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[2] McDonagh TA, et al. (2021) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* Sep 21;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368. Erratum in: Eur Heart J. 2021 Oct 14;: PMID: 34447992.

MSAC noted the claim that cardiac MRI was likely superior in terms of diagnostic accuracy and prognosis compared with clinical criteria and EMB. MSAC noted that no direct test-to-health outcomes evidence was identified for cardiac MRI in the diagnosis of acute myocarditis and populations 1 and 2 could not be disaggregated in the evidence. Therefore, a linked evidence approach was used for undertaking the assessment.

MSAC noted that in the combined analysis ESC considered, cardiac MRI showed higher sensitivity and specificity than EMB.

MSAC noted that the linked evidence showed that:

- for population 1, although MRI findings could help stratify risk, there were no clear guidelines on how myocarditis patients should be monitored or managed.
- for population 2, cardiac MRI could reduce the use of coronary CT (to rule out CAD) by confirming diagnosis of myocarditis through exclusion, and it could allow avoiding unnecessary medications (anti-platelet therapy). However, this was highly uncertain, due to the low-quality evidence presented.

MSAC concluded that cardiac MRI was likely superior in terms of diagnostic accuracy and ability to make a prognosis compared with clinical criteria and EMB. However, MSAC noted that there was no evidence of change in management or improved health outcomes as a result of cardiac MRI. Therefore, MSAC considered non-inferior effectiveness might be more appropriate, although on balance MSAC was confident that there would be a change in management following cardiac MRI based on it being widely recommended for this purpose in clinical guidelines, and so overall advised that cardiac MRI in population 1 was acceptably effective. Due to the lack of evidence and guidelines for management for those patients in whom cardiac MRI detects LGE changes, MSAC considered the value of knowing for diagnosis of myocarditis was also uncertain. However, MSAC considered there was an unmet clinical need for improved diagnosis of myocarditis.

MSAC noted that the applicant advised that cardiac MRI service is a complex test and should be performed and reported by those radiologists and cardiologists who have been certified by the Conjoint Committee for Certification in cardiac MRI. MSAC considered that specialists other than radiologists and cardiologists (such as nuclear physicians) who have extended their training to perform cardiac MRI should also be able to provide this service. MSAC considered that requiring Conjoint Committee credentialling may be reasonable as not all radiologists and other specialists will be able to provide cardiac MRI, although noted that doing so may limit patient access to services in regional and rural areas. On balance, MSAC considered that the service should be reported by a specialist or consultant physician who has been certified by the Conjoint Committee for Certification in cardiac MRI, although noted policy advice that certification requirements are rules in the Diagnostic Imaging Services Table rather than the item descriptor, therefore advised it was not appropriate for the certification requirement to be included in the item descriptor. MSAC's supported item descriptor is provided above (Table 1), and MSAC noted the Department will consult further with the sector on this matter.

MSAC noted that the proposed fee matched the fee for the temporary cardiac MRI item (Item 63399), which was $904.70 (to be indexed from 1 July 2024). This temporary fee was implemented following sector advice during the pandemic that benchmarked the fee to MBS items such as 63395, the current item for assessment of myocardial structure and function in the setting of arrhythmogenic right ventricular cardiomyopathy. MSAC noted that at its February 2024 meeting ESC considered that implementing temporary item 63399 was a matter of urgency during the pandemic, but considered the current fee was too high for the resources required, and relativity to other cardiac MRI items could not be used to determine an appropriate fee for MSAC's supported item descriptor. MSAC considered that the fees for different MRI items are currently mis-aligned, and that the fees should be aligned between comparable cardiac MRI

MBS items. The Department advised MSAC that it will review the current fees of cardiac MRI MBS items. MSAC considered that if the proposed item for ACS for population 2 was not funded, there would be a service gap for patients who were currently able to access cardiac MRI under MBS item 63399. MSAC noted and also agreed with the pre-MSAC response that myocarditis induced by vaccines or immune checkpoint inhibitors would be covered by the proposed MBS item for population 1. In the context of the current utilisation of MBS item 63399, MSAC considered the service gap was acceptably small. To ensure cardiac MRI adequately encompassed the supported population MSAC advised that department should monitor the item post implementation.

MSAC noted that the economic evaluation was a cost-utility analysis of the proposed MBS listing in the two populations of interest. MSAC considered this was appropriate. However, MSAC considered that the economic evaluation was highly uncertain. There were lack of local prevalence and incidence data for myocarditis in Australia; therefore, the economic evaluation was based on international sources. In the absence of evidence about the change of management with LGE changes and the relative effectiveness of regular monitoring compared to standard care, expert opinion was used to inform these input parameters in the model, which MSAC (agreeing with ESC) considered made the economic results highly uncertain.

MSAC noted that the management pathway with cardiac MRI resulted in an incremental cost-effectiveness ratio (ICER) of $66,356 per quality-adjust life-year (QALY) in population 1. MSAC considered this result might have been primarily driven by the absence of a comparable investigative health technology to contrast the increased cost of cardiac MRI for the diagnosis or exclusion of myocarditis in the current management pathway. MSAC advised cardiac MRI in population 1 was acceptably cost-effective.

In population 2, the management pathway with cardiac MRI resulted in an ICER of $15,787/QALY gained. The improved value for money of cardiac MRI in population 2 was likely driven by the prognostic value of cardiac MRI in highlighting patients with fibrosis via the presence of LGE and the potential risk reduction of a downstream major adverse cardiac events (MACE) in these patients via monitoring. The avoidable costs of placing potential myocarditis patients on prophylactic ACS medications was another factor that contributed to the cost-effectiveness of cardiac MRI in this population. However, the model assumed that cardiac MRI would replace other imaging, which as above MSAC considered would not take place in the real world, and so the claimed cost-offsets would not be realised. MSAC advised the cost-effectiveness of cardiac MRI in population 2 was highly uncertain due to lack of local data and the modelling having over-estimated the cost-offsets.

MSAC noted that the DCAR used an epidemiological approach to estimate the expected extent of usage and the financial implications of listing cardiac MRI on the MBS. This approach was chosen instead of a market-based approach because the MBS items for the comparator tests (for example, EMB, CTCA, TTE) was not restricted to the proposed population. MSAC noted that for population 1, the net financial impact to the MBS was $3,685,782 (year 1) and $3,951,052 (year 6); for population 2 the net cost to the MBS was $1,401,494 (year 1) and $1,502,361 (year 6), which was based on a cost of cardiac MRI around $15 million per year, and cost-offsets from other services replaced of around $14 million per year. MSAC noted that if no cost-offsets were assumed for populations 1 and 2, the net financial impact to the MBS remained at $3.6-$3.9 million for population 1, but increased from $1.4-1.5 million to $14.7-15.8 million for population 2.

MSAC considered that the estimations of the extent of use and financial implications of cardiac MRI were highly uncertain due to numerous assumptions that were required to estimate the financial impact. MSAC noted the lack of Australian prevalence and incidence data for

myocarditis and the uncertainty in the size of the eligible population that was estimated to be approximately 7,900 cases per year. Furthermore, the financial estimates were also sensitive to incidence of myocarditis, proportion of patients in populations 1 and 2, and uptake rate of cardiac MRI. MSAC also noted the assessment had not taken into account additional testing that may be occurring through the private health system. Despite the relative uncertainty in the estimated cost, MSAC advised the financial impact for the supported cardiac MRI was modest and acceptable. To mitigate uncertainty, MSAC recommended utilisation should be reviewed after two years of listing.

4.   Background

In April 2017, MSAC considered the following application for cardiac MRI related to the diagnosis of myocarditis:

- Application 1432 – cardiac MRI of patients with suspected non-ischaemic cardiomyopathy (Part B).

MSAC had not previously considered cardiac MRI for the diagnosis of myocarditis. However, Population 5 of Application 1432 included patients with cardiomyopathies due to acute coronary syndrome (ACS), myocarditis or Takotsubo cardiomyopathy (TTC).

MSAC was unable to determine the benefit of cardiac MRI compared with prior testing alone in Population 5 due to the limited evidence base around diagnostic accuracy. While accepting that cardiac MRI could clarify diagnoses and change management, largely by ruling out ACS and reducing or ceasing medicines to treat ACS, this was based on low-quality case series evidence. The result of the cost-effectiveness analysis in this population was highly uncertain, difficult to interpret and did not capture all relevant patient outcomes. Only two out of six proposed populations (arrhythmogenic right ventricular cardiomyopathy [ARVC] and first-degree relatives of ARVC patients) were identified as potentially benefiting from cardiac MRI in Application 1432. Cardiac MRI for the diagnosis of ARVC (MBS item 63395) and MRI scan of cardiovascular system for first degree relatives of ARVC patients (MBS item 63397) were listed on the MBS on May 1, 2018.

5.   Prerequisites to implementation of any funding advice

The Applicant advised that the proposed cardiac MRI service is a complex test and should be limited to only those radiologists and cardiologists who have been certified by the Conjoint Committee for Certification in cardiac MRI.

6.   Proposal for public funding

A new MBS item was proposed for cardiac MRI, with the fee informed by the temporary MBS item for the diagnosis of mRNA vaccine-associated myocarditis (MBS item 63399) (Table 2). The MBS item fee also included the fee of standard item for gadolinium based contrast agent (GBCA) (MBS item 63491; $47.40 as of 1 November 2023), given GBCA would be used as standard (unless contraindicated).

Table 2   Proposed MBS item descriptor for cardiac MRI

Category 5 – DIAGNOSTIC IMAGING SERVICES – Group I5 – Magnetic resonance imaging

MBS item *XXXX
 	
Proposed item descriptor: MRI scan of cardiovascular system for the assessment of myocardial structure and function and characterisation, if the service is requested by a specialist or consultant physician who has assessed the patient, and the request for the scan indicates:
 	
    (a) the patient has acute onset (<3 months) of heart failure or unexplained arrhythmia suspected due to myocarditis and would otherwise require endomyocardial biopsy to confirm the diagnosis; OR
 	
    (b) the patient has acute onset of chest pain suspected due to myocarditis, <u>with an intermediate risk of obstructive coronary artery disease (CAD),</u> on the basis of:
 	
        (i) Elevated troponin, OR
 	
        (ii) Abnormal electrocardiogram, AND
 	
        (iii) there are no other features of an acute coronary syndrome identified on clinical history, examination, or with the above investigations.
 	
        <u>(iv) the purpose of cardiac MRI in this population is to diagnose myocarditis and not to rule out CAD.</u>

(R) (Anaes.) (Contrast)
Fee: $904.70 Benefit: 75% = $678.55 85% = $806.00 Plus: GBCA MBS item 63491: Fee: $47.40 Benefit: 75% = $35.55 85% = $40.30
<u>Practice Note:</u> <u>Intermediate risk of obstructive coronary artery disease (CAD) should be determined based on the current National Heart Foundation (NHF) and Cardiac Society of Australia and New Zealand (CSANZ) guidelines.</u>

CSANZ = Cardiac Society of Australia and New Zealand; GBCA = gadolinium-based contrast agent; MBS = Medicare Benefits Schedule; NHF = National Heart Foundation-.
Note: 85% benefit reflects the 1 November 2023 Greatest Permissible Gap (GPG) of $98.70. All out-of-hospital Medicare services that have an MBS fee of $658.35 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
Note: At the time of December 2022 PASC meeting, the MBS item fee for the temporary cardiac MRI was $868.90; however, the fee has since increased with indexation to $904.70 as of 1 November 2023.
Source: PASC's revised MBS item descriptor, 1713 PICO pg 43. Additions proposed by the DCAR are shown in underlined font.

7.   Population

Myocarditis is defined clinically as the inflammation of the myocardium. It may result from infectious and non-infectious causes. Acute myocarditis is the most common type of myocarditis (65% of cases) and can be defined as a period of <1 month between symptom onset and diagnosis with increased level of high sensitivity troponin. Globally, it is estimated that the worldwide prevalence of myocarditis is 1.5 million patients, with 10-22 new cases diagnosed per 100,000 population annually. In Australia, there were no detailed data on the prevalence or incidence of myocarditis in the general population. A recent systematic analysis of Global Burden of Disease (2019) estimated 6,220 (95% CI: 5,000 to 7,530) incident cases of myocarditis in Australasia in 2019[3].

The diagnosis of myocarditis is often challenging due to the variety of aetiologies, clinical presentations and diagnostic approaches. The use of cardiac MRI in diagnosis of acute myocarditis was proposed in the following two populations:

- Population 1: Patients with signs and symptoms of acute onset cardiomyopathy (acute heart failure and/or arrythmia) suggestive of acute myocarditis.

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[3] Wang, Y.-W.-Y., et al. (2023). Global, regional, and national burdens of myocarditis, 1990–2019: systematic analysis from GBD 2019. *BMC Public Health*, 23(1), 714.

All patients presenting with acute onset cardiomyopathy are considered eligible for cardiac MRI to differentiate those with myocarditis from those without myocarditis. However, cardiac MRI cannot completely replace endomyocardial biopsy (EMB) in making a definitive diagnosis of myocarditis. Furthermore, EMB cannot be replaced by cardiac MRI for a small group of patients, including those who are severely unwell with end-stage heart failure indicated for heart transplantation or those who are haemodynamically unstable.

- Population 2: Patients presenting with signs and symptoms of acute coronary syndrome with an intermediate risk of obstructive coronary artery disease, or suspected myocarditis.

In this population, myocarditis is a diagnosis of exclusion of obstructive CAD, with invasive coronary angiography (ICA) or computed tomography coronary angiography (CTCA) or other investigations such as transthoracic echocardiogram (TTE). The application stated that in clinical practice, patients classified with a low pre-test likelihood of CAD would not receive ICA or CTCA to exclude or confirm obstructive CAD. Instead, they would undergo cardiac MRI as the initial diagnostic procedure. If myocarditis was diagnosed following cardiac MRI, further investigations to rule out obstructive CAD would not be necessary.

8.   Comparator

The applicant proposed different comparators for cardiac MRI for the two populations:

In Population 1, the comparator for patients with signs and symptoms of cardiomyopathy was standard management (e.g., anti-failure treatment, circulatory support, antiarrhythmic treatment) for clinically suspected acute myocarditis with or without EMB when clinically indicated. The applicant indicated that the reference standard for the assessment of diagnostic accuracy may be either EMB or clinical criteria (i.e., a combination of clinical, laboratory, echocardiography and angiographic findings). The DCAR considered this was appropriate given that EMB is an invasive procedure and may not be used routinely in practice; therefore, the reference standard for the assessment of diagnostic accuracy may be either EMB or clinical criteria (i.e., a combination of clinical, laboratory, echocardiography and angiographic findings). In Australian clinical practice, EMB via cardiac catheterisation is reimbursed under MBS item 38275.

In Population 2, for patients with signs and symptoms of ACS, the comparator suggested by the applicant was standard management of intermediate-risk ACS including CTCA/ICA to exclude obstructive CAD ± TTE. The PICO stated it was important to note that ICA and CTCA are diagnostic methodologies to ascertain some of the differential diagnoses of myocarditis, whereas cardiac MRI can detect myocarditis in a more direct manner. Therefore, such a comparison may not be direct in terms of quantitative evidence for diagnostic accuracy outcomes. Therefore, PASC considered a more appropriate comparator could be standard management for clinically suspected acute myocarditis with/without EMB when clinically indicated. Of note, it was expected that cardiac MRI may reduce the utilisation of CTCA/ICA in this population, which was captured in the decision model presented in this report. In Australian clinical practice, ICA is reimbursed under MBS item 38244, CTCA is reimbursed under MBS item 57360, and TTE is reimbursed under MBS Item 55126.

9.   Summary of public consultation input

Consultation input was received from six (6) professional organisations, two (2) consumer organisations and seven (7) individuals, of which six (6) were specialists and one (1) a family member of a consumer.

The eight (8) organisations that submitted inputs were:
- Cardiomyopathy Association of Australia
- Australian Society of Medical Imaging and Radiation Therapy (ASMIRT)
- Australian Diagnostic Imaging Association
- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Society for Cardiovascular Magnetic Resonance (SCMR)
- International Society for MR Radiographers and Technologists (ISMRT)
- National Heart Foundation of Australia
- Australian Technical Advisory Group on Immunisation (ATAGI)

The consultation feedback from organisations and individuals was generally supportive of the application, and unanimously agreed with the clinical need and public health significance of publicly funding this application.

The applicant's pre-MSAC response also provided a letter of support from Cardiac Society of Australia and New Zealand (CSANZ).

Benefits:
- MRI is considered to be the most reliable non-invasive method of diagnosing myocarditis, allowing for earlier diagnosis and treatment and reducing need for downstream testing
- Improved safety compared to the comparator, as MRI does not expose patients or physicians to harmful radiation and there are no known long-term adverse effects of MRI
- Diagnostic certainty from excellent sensitivity and specificity of the proposed service, which may also provide alternate diagnoses
- Few contraindications and very well tolerated by patients
- The procedure will reduce the number of coronary angiographies and myocardial biopsies that will need to be performed on patients as it can act as gatekeeper to identify more appropriate patients for such invasive procedures
- Equity of access, as currently patients are required to either wait 3 months through the public system or pay the fee out of pocket.
- A cardiac MRI national database of presumed and confirmed myocarditis scans would allow for further research and understanding of the pathology
- More cost effective

Disadvantages
- Subspecialised training and equipment are required for conducting cardiac MRI, therefore certification requirements for reporting and providing cardiac MRI service may need to be considered.
- An increase in the cost of imaging
- Some patients may have MRI-Incompatible implanted devices, allergies to contrast, or suffer from claustrophobia which may impact their ability to have an MRI test

Other feedback
Cardiac MRI was described as 'the gold standard' for the diagnosis of myocarditis by multiple respondents.

The proposed service descriptor does not include the urgent requirement for patients referred by medical oncologists regarding immunotherapy induced myocarditis and that the true cost of the proposed service is closer to $900-$1000.

There was concern that the provider requirement for recognition by the Conjoint Committee in Cardiac MRI (CCCMRI), as proposed in the application will severely limit patient access and result in a serious underutilisation of the item.

Targeted consultation feedback was received from SCMR who raised the following key points:
- Population 2 could be further defined by adequate clinical workup to exclude patients with a moderate-high likelihood of ACS noting that:
  - Patients with a moderate-high likelihood of ACS should be considered for cardiac MRI if the ischemia work up is negative or equivocal
  - Patients with a similar likelihood of ACS versus myocarditis require clinical judgement and should be considered for cardiac MRI prior to ischemia work up if stable without ongoing chest pain – noting this may obviate the need for invasive testing
- Examples of when cardiac MRI is indicated for both population groups could not be refined solely by duration of patient. SCMR referred to the American Heart Association (AHA) 2020 Expert Consensus Document on Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy to provide definitions of acute, chronic, and chronic inflammatory cardiomyopathy that includes symptom duration.

10. Characteristics of the evidence base

No direct test to health outcomes evidence was identified for cardiac MRI in the diagnosis of acute myocarditis. Therefore, a linked evidence approach was used for undertaking the assessment.

- consideration of the diagnostic accuracy of cardiac MRI compared with EMB/clinical criteria;
- consideration of the prognostic value (longitudinal accuracy) of cardiac MRI in patients with suspected or acute myocarditis, clinical utility of the investigative medical service in terms of impact on patient management, and the impact on health outcomes; and
- consideration of the relative safety of performing the cardiac MRI compared with reference standard EMB/clinical criteria, both the immediate safety issues of directly performing the test and 'flow on' safety issues that arise as a result of conducting cardiac MRI.

Key features of the included evidence

Table 3 summarises the key features of the included evidence.

Table 3   Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Accuracy and performance of the test (cross-sectional accuracy)	Systematic reviews and meta-analyses	☒ k=5 n=7522	All five systematic reviews with high risk of bias
	16 individual studies	☒ k=16 n=1246	Nine studies were considered low risk of bias. The other seven studies included only one domain with high risk of bias and the remaining three domains are low risk or unclear risk of bias.
Prognostic evidence (longitudinal accuracy)	Systematic reviews and meta-analyses	☒ k=2 n=3647	Moderate
	9 individual studies	☒ k=9 n=2139	Seven out of nine of studies were included in the above mentioned two systematic reviews
Change in patient management	No evidence specifically related to the impact on patient management of using cardiac MRI in patients with acute myocarditis identified in the scoping review	☐ k=0 n=0	NA
Health outcomes	No evidence specifically related to the impact on health outcomes of using cardiac MRI in patients with acute myocarditis identified in the scoping review.	☐ k=0 n=0	NA

k = number of studies; n = number of patients; NA = not applicable

The diagnostic accuracy of cardiac MRI compared with EMB/clinical criteria (Cross sectional accuracy)

The evidence for the cross-sectional accuracy were provided using an updated systematic review (SR) based on Kotanidis et al. (2018)[4] , which included cardiac MRI studies for the diagnosis of acute myocarditis in adult patients up to 2017. The updated SR by the Assessment group identified a total of 21 additional studies (16 studies and 5 SRs) from 2017 to 2023. All five SRs identified in the updated SR had critical weakness in one or more domains, therefore, all five SRs were considered high risk of bias based on the AMSTAR (A Measurement Tool to Assess systematic Reviews) checklist[5]. All 16 individual studies identified in the updated SR used 1.5-T or higher gadolinium-based MRI scanner systems. The key outcomes in all studies were sensitivity and specificity of cardiac MRI. The risk of bias for these 16 studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. Based on the risk of bias analyses, nine studies were considered low risk of bias. The other seven studies included only one domain with high risk of bias and the remaining three domains were low risk or unclear risk of bias.

Prognostic value (longitudinal accuracy) of cardiac MRI

A scoping review of published literature was undertaken to identify the prognostic value (longitudinal accuracy) of cardiac MRI in patients with suspected or acute myocarditis. Late

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[4] Kotanidis, C. P et al (2018). Diagnostic Accuracy of Cardiovascular Magnetic Resonance in Acute Myocarditis: A Systematic Review and Meta-Analysis [Article]. *JACC: Cardiovasc Imaging*, 11(11), 1583-1590.

[5] Shea, B. J., et al (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*, 358, j4008.

gadolinium enhancement (LGE) has been shown to be the strongest independent predictor of outcome with a hazard ratio (HR) of 8.4 for all-cause mortality and 12.8 for cardiac mortality[6]. As a result, the scoping review focused on the prognostic value of LGE with cardiac MRI in patients with suspected or acute myocarditis. The scoping review identified nine studies and two systematic reviews. Most of the studies (7/9) identified in the scoping review were meta-analysed by two systematic reviews[7] (Georgiopoulos, G et al 2021) that provided summary statistics for the prognostic value of cardiac MRI for predicting health outcomes.

Linked evidence of change in management

There was no evidence specifically related to the impact on patient management of using cardiac MRI in patients with acute myocarditis identified in the scoping review. The impairment of LVEF, the presence of extensive LGE, oedema, and diffuse fibrosis on cardiac MRI all contribute to a heightened risk of adverse outcomes, thus findings of the cardiac MRI can help to risk stratify patients[8]. However, the assessment group noted there were no current clear guidelines on how myocarditis should be monitored, despite evidence showing that approximately 50% of patients with complicated myocarditis do not achieve a full recovery.

For Population 1, cardiac MRI informed the diagnosis and the presence of fibrosis, linked to major adverse cardiovascular events (MACE) (Grani et al. 2017); however, there were no clear recommendations from existing guidelines about monitoring and or change of management for patients with fibrosis[7].

For Population 2, cardiac MRI could reduce the use of CTCA, a diagnostic procedure used in patients with signs and symptoms of ACS to rule out CAD and confirm the diagnosis of myocarditis through exclusion. Cardiac MRI may also help confirm myocarditis in patients who are suspected to have myocardial infarction with non-obstructive coronary arteries (MINOCA), thus eliminating the need for unnecessary medications and providing a more accurate diagnosis and tailored treatment approach[9].

Linked evidence of health outcomes

There was no evidence specifically related to the impact on health outcomes of using cardiac MRI in patients with acute myocarditis identified in the scoping review.

11. Comparative safety

No comparative safety studies were identified in the literature search for the safety of cardiac MRI imaging. The studies included in the updated systematic review comparing the diagnostic accuracy of cardiac MRI and EMB were mostly single modality studies, where the patients were only imaged once with cardiac MRI. None of these studies reported adverse events due to cardiac MRI. As there were no direct comparative studies relating to safety in this patient cohort,

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[6] Grün, S., et al (2012). Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. *J Am Coll Cardiol* , 59(18), 1604-1615.

[7] Yang, F., et al (2020). The prognostic value of late gadolinium enhancement in myocarditis and clinically suspected myocarditis: systematic review and meta-analysis. *Eur Radiol*, 30(5), 2616-2626.

[8] Eichhorn, C. et al. (2022). Multiparametric Cardiovascular Magnetic Resonance Approach in Diagnosing, Monitoring, and Prognostication of Myocarditis. *JACC Cardiovasc Imaging*., 15(7), 1325-1338.

[9] Liang, K., et al. (2022). The Role of Cardiac Magnetic Resonance in Myocardial Infarction and Non-obstructive Coronary Arteries, *Front Cardiovasc Med*, 17(8)

the DCAR assessed safety using general safety data available for MRI and EMB. Information was sourced from authoritative information websites and clinical guidelines.

Cardiac MRI is a safe and non-invasive test for most people. Being a non-invasive test without any associated radiation and limited nephrotoxicity, cardiac MRI has a good safety profile[10]. The only concern is that people with any type of metal device including cardiac devices (e.g., pacemakers and defibrillators) inside their body should be evaluated for MRI compatibility of the device prior to the procedure. There are growing body of literature in recent past evaluating the safety of cardiac MRI in the presence of other medical devices[11,12]. In Australia, MRI safety related assessment of implants or devices is available via http://www.mrisafety.com/TMDL_list.php.

In addition, gadolinium-based contrast agent (GBCA) is relatively safe; however, a rare acute allergy-like reaction can occur in approximately 0.07% of patients. Also, a small proportion of patients who have claustrophobia may have difficulty undergoing cardiac MRI, given the narrow diameter of the scanner and the long examination time. Cardiac MRI is superior in terms of safety compared to EMB as cardiac MRI is associated with decreased adverse effects[13]. CTCA and MRI have similar safety implications relating to the use of contrast agents, but the main difference is that CTCA exposes patients to ionising radiation, which increases the lifetime risk of radiation-induced cancer. Therefore, cardiac MRI is safer compared with CTCA because of the lack of ionising radiation and therefore lower associated cancer risk. Furthermore, MRI imaging is undertaken widely in Australia for other conditions and the safety profile for them is generally accepted, with individual clinicians responsible for assessing the risk-benefit ratio for their patient's circumstances.

12. Comparative effectiveness

The diagnostic accuracy of cardiac MRI compared with EMB/clinical criteria (Cross sectional accuracy)

Four cardiac MRI index tests were considered: T1 mapping, T2 mapping, LGE, and LLC as interested in this application. The primary measures were sensitivity and specificity. All 5 systematic reviews and 16 individual studies identified in the updated systematic review had reported the sensitivity and specificity for the four index tests mentioned above and these values were obtained during data extraction. No studies were identified that compared the diagnostic performance of cardiac MRI separately for Population 1 and 2 as specified in the ratified PICO. Instead, the study populations were defined broadly as patients suspected with acute myocarditis. Study details and results were therefore reported representing both Populations 1 and 2.

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[10] Naehle, C. P., et al. (2011). Safety, feasibility, and diagnostic value of cardiac magnetic resonance imaging in patients with cardiac pacemakers and implantable cardioverters/defibrillators at 1.5 T. *Am Heart J*, 161(6), 1096-1105.

[11] Dacher, J. N., et al. (2023). Safety and performance of MR-conditional pacing systems with automated MRI mode at 1.5 and 3 Tesla. *Eur Radiol*, 33(10), 6948-6958.

[12] Yang, E., et al. (2022). Magnetic resonance imaging safety in patients with cardiac implantable electronic devices. *Trends Cardiovasc Med*, 32(7), 440-447. https://doi.org/https://doi.org/10.1016/j.tcm.2021.08.001

[13] Kiamanesh, O., et al. (2020). The State of the Heart Biopsy: A Clinical Review. *CJC Open*, 3(4), 524-531.

Evidence from the five systematic reviews

Table 4 summarises the results reported in the systematic reviews for diagnostic accuracy of each index test in cardiac MRI.

Table 4   Results reported in the systematic reviews

Analysis	K	N	Sensitivity	Specificity	AUC	Diagnostic Odds Ratio	Positive Likelihood Ratio	Negative Likelihood Ratio
Native T1 mapping								
Blissett et al. 2019	9	560	0.82	0.87	NR	NR	NR	NR
Jia et al. 2019	8	582	0.84 (0.78-0.88)	0.86 (0.69-0.95)	NR	NR	NR	NR
Kotanidis et al. 2018	7	583	0.89 (0.79–0.94)	0.90 (0.78–0.96)	0.95 (0.93–0.97)	71.31 (17.7-287.22)	8.87 (3.69–21.34)	0.12 (0.06-0.26)
Pan et al. 2018	8	694	0.83 (0.79-0.87)	0.87 (0.83-0.90)	NR	44.1 (18.4-105.4)	6.2 (3.4-11.0)	0.15 (0.07-0.32)
T2 mapping								
Blissett et al. 2019	8	514	0.75	0.84	NR	NR	NR	NR
Jia et al. 2019	7	455	0.77 (0.69-0.83)	0.83 (0.73-0.89)	NR	NR	NR	NR
Kotanidis et al. 2018	6	381	0.78 (0.65–0.87)	0.84 (0.72–0.92)	0.88 (0.85–0.91)	19.19 (10.37-5.46)	4.97 (2.92–8.44)	0.26 (0.16–.41)
Pan et al. 2018	6	421	0.71 (0.65-0.76)	0.84 (0.76-0.89)	NR	18.6 (10.0-34.5)	4.1 (2.4-7.0)	0.29 (0.18-0.47)
Late gadolinium enhancement								
Blissett et al. 2019	52	3557	0.69	0.95	NR	NR	NR	NR
Kotanidis et al. 2018	17	1308	0.68 (0.56–0.77)	0.96 (0.87–0.99)	0.87 (0.84–0.90)	54.26 (12.38–237.78)	18.64 (4.93–70.43)	0.34 (0.24–.47)
Wei et al. 2017	9	614	0.70 (0.52-0.83)	0.57 (0.41-0.72)	0.67 (0.63-0.71)	3.0 (1.0-8.0)	1.6 (1.1-2.4)	0.52 (0.30-0.92)
Lake Louise criteria								
Blissett et al. 2019	NR	NR	0.78	0.74	NR	NR	NR	NR
Pan et al. 2018	13	1022	0.75 (0.71-0.78)	0.87 (0.84-0.90)	NR	24.0 (10.1-56.8)	6.2 (3.1-12.3)	0.31 (0.25-0.39)
Kotanidis et al. 2018	8	577	0.78 (0.72–0.83)	0.88 (0.68–0.96)	0.83 (0.79–0.86)	26.78 (7.65–3.76)	6.64 (2.20–20.10)	0.25 (0.19–.32)
Wei et al. 2017	7	417	0.70 (0.62-0.76)	0.56 (0.31-0.78)	0.70 (0.66-0.74)	3.0 (1.0-8.0)	1.6 (0.9-2.8)	0.54 (0.35-0.84)

AUC = area under curve; K = number of studies; NR=not reported
Notes: numbers in parentheses are 95% confidence interval

All systematic reviews reported higher sensitivity and specificity for each index test. The systematic review by Wei et al. (2017) included studies with EMB only as reference standard. This systematic review reported the lowest sensitivity and specificity values for LLC compared to the values reported in the other systematic reviews.

Evidence from the meta-analysis of individual studies

The assessment group conducted a meta-analysis to assess the diagnostic test accuracy of cardiac MRI related to the four index tests compared with clinical criteria/EMB in the diagnosis of acute myocarditis. This meta-analysis included the 16 studies identified from the updated systematic review and the 22 studies included in the systematic review conducted by Kotanidis et al. (2018). Results were reported separately for the 16 individual studies identified from the updated systematic review and the combined analysis using both reviews (i.e., from the updated SR and Kotanidis et al. (2018)). Given that the included studies had used different thresholds to dichotomise test results measured on a continuous scale and therefore meta-analyses using hierarchical models to produce summary receiver operating curve (HSROC) curves and 95% prediction regions for each index test were performed using Stata version 17[14]. Table 5 summarises the overall results of meta-analyses conducted using the individual papers identified in the updated systematic reviews and the papers included in the Kotanidis et al. (2018).

Table 5   Overall Results of Meta-Analyses Conducted

Index Test	K	N	TP	TN	Sensitivity	Specificity	Diagnostic Odds Ratio	Positive Likelihood Ratio	Negative Likelihood Ratio
Native T1 mapping									
Studies from updated SR	9	618	337	168	0.81 (0.76-0.85)	0.86 (0.75-0.85)	25.43 (10.62-60.90)	5.45 (3.01-10.61)	0.22 (0.16-0.30)
Combined analysis	16	1236	623	381	0.85 (0.79-0.89)	0.88 (0.80-0.93)	39.75 (18.11-87.24)	6.9 (4.07-11.71)	0.17 (0.12-0.24)
T2 mapping									
Studies from updated SR	10	663	327	182	0.77 (0.67-0.84)	0.82 (0.74-0.87)	14.59 (6.72-31.67)	4.17 (2.75-6.32)	0.28 (0.19-0.43)
Combined analysis	16	1072	492	310	0.78 (0.70-0.83)	0.83 (0.77-0.87)	16.47 (9.61-28.22)	4.46 (3.25-6.13)	0.27 (0.20-0.37)
Late gadolinium enhancement									
Studies from updated SR	9	718	331	188	0.75 (0.64-0.83)	0.94 (0.72-0.99)	48.24 (9.78- 238.03)	12.89 (2.42-68.63)	0.27 (0.19-0.37)
Combined analysis	26	2026	862	632	0.70 (0.62-0.78)	0.96 (0.88- 0.98)	50.95 (17.33-149.76)	15.74 (5.83-42.49)	0.30 (0.24-4.19)

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[14] StataCorp. (2021). Stata Statistical Software: Release 17. In StataCorp LLC

Index Test	K	N	TP	TN	Sensitivity	Specificity	Diagnostic Odds Ratio	Positive Likelihood Ratio	Negative Likelihood Ratio
Lake Louise criteria									
Studies from updated SR	10	736	354	206	0.70 (0.60-0.78)	0.94 (0.82-0.98)	34.73 (9.91-121.63)	11.05 (3.74-32.63)	0.31 (0.23-0.44)
Combined analysis	18	1313	637	387	0.74 (0.68-0.79)	0.92 (0.82-0.96)	31.76 (12.95-77.89)	8.97 (4.04-19.91)	0.28 (0.22-0.35)

K = number of studies; N = number; SR = systematic review; TP = true positive; TN = true negative.

Notes: numbers in parentheses are 95% confidence intervals

All index tests of cardiac MRI reported positive likelihood ratio>5 and negative likelihood ratio<1, indicating stronger diagnostic ability.

Summary of findings of cross-sectional accuracy

The assessment group found cardiac MRI was reasonably good at diagnosing acute myocarditis as it was associated with high sensitivity and specificity. The meta-analysis based on the 16 individual studies reported high sensitivity and specificity values and of these studies, nine studies were low risk of bias. Therefore, based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tool, quality of evidence for diagnostic accuracy provided in meta-analysis of 16 individual studies was moderate. Of note, the five systematic reviews including Kotanidis et al. (2018) also reported high sensitivity and specificity for cardiac MRI. However, these systematic reviews and most of the studies included in the Kotanidis et al. (2018) were of high risk of bias. Therefore, based on the GRADE tool, quality of evidence for diagnostic accuracy provided in these systematic reviews and combined analysis was very low.

None of the included studies were conducted in the Australian setting. Study participants were predominantly male, with a mean age between 31 and 46 years for studies conducted in adults. The Australian Institute of Health and Welfare (AIHW) had not reported data on myocarditis patients specifically. In patients with cardiovascular disease, it reported that 15.7% were between the aged of 18 and 54. Further, 44% of cardiovascular disease patients in Australia were female, which was larger than the proportion of female patients in most of the studies. Only one study reported additional behavioural and health-related demographic information. In Baessler et al. (2019), 38% of patients were smokers and 57% had hypertension. This was comparable to the Australian population, in which these values were 23% and 53% respectively, for individuals with cardiovascular disease[15].

Globally, it is estimated that the worldwide prevalence of myocarditis is 1.5 million patients, with 10-22 new cases diagnosed per 100,000 population annually.[16] However, the assessment group noted there was no detailed data on the incidence and prevalence of myocarditis among Australian general population. The Australian data for myocarditis were mainly available for the incidence post mRNA COVID vaccine. According to the applicant, while the Australian prevalence

[15] Australian Institute of Health and Welfare. (2023). Data tables: Heart, stroke and vascular disease Australian facts. https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/hsvd-facts/data

[16] Global Burden of Disease Study 2013 Collaborators. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*, 386(9995), 743-800.

and incidence of myocarditis considered in the Application was uncertain, it had been reasonably estimated that the overall incidence of myocarditis in the community was approximately 30 per 100,000-person years; a rate of 0.03%[17]. Considering the 26,473,055 Australian population in 2023 based on Australian Bureau of Statistics (ABS) data, there would be a possible 7,941 myocarditis cases per year. The applicant estimation was close to the values reported for the myocarditis incidence cases 6,222 (5,000-7,530) in Australasia region in 2019 (Wang, Y.-W.-Y et al 2023) As myocarditis is usually self-limiting and resolves within a few months for most patients, it was considerable to assume that the incidence rate is approximate to the prevalence rate.

The updated systematic review did not identify any individual studies conducted in the Australian setting. However, the assessment noted that the application of meta-analysis data from the individual studies of updated systematic review (the most recent papers) and the 0.03% prevalence for the Australian setting, all four index tests of cardiac MRI yielded high sensitivity and specificity Table 6. The assessment group considered this indicated that even with the low prevalence in Australian setting, cardiac MRI yielded high sensitivity and specificity.

Table 6   Application of cardiac MRI in the Australian setting based on the meta-analysis results of 16 individual studies

Index Test	K	N	TP	TN	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
Native T1 mapping	9	618	337	168	0.80 (0.76-0.84)	0.84 (0.79-0.89)	0.001 (0.001 -0.002)	0.99 (0.99-0.99)	5.3 (3.80-7.39)	0.23 (0.19-0.28)
T2 mapping	10	663	327	182	0.75 (0.70-0.78)	0.81 (0.75-0.86)	0. 001 (0.0009 -0.001)	0.99 (0.99-0.99)	3.97 (3.00-5.25)	0.31 (0.26-0.37)
LGE	9	718	331	188	0.68 (0.64-0.72)	0.80 (0.75-0.85)	0.001 (0.0008 -0.001)	0.99 (0.99-0.99)	3.48 (2.67-4.54)	0.39 (0.34-0.46)
LLC	10	736	354	206	0.69 (0.65 -0.73)	0.92 (0.87-0.95)	0.002 (0.001 -0.003)	0.99 (0.99-0.99)	8.20 (5.31-12.66)	0.34 (0.29-0.38)

LLC = Lake Louise criteria; LGE = Late gadolinium enhancement; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.
Notes: numbers in parentheses are 95% confidence intervals

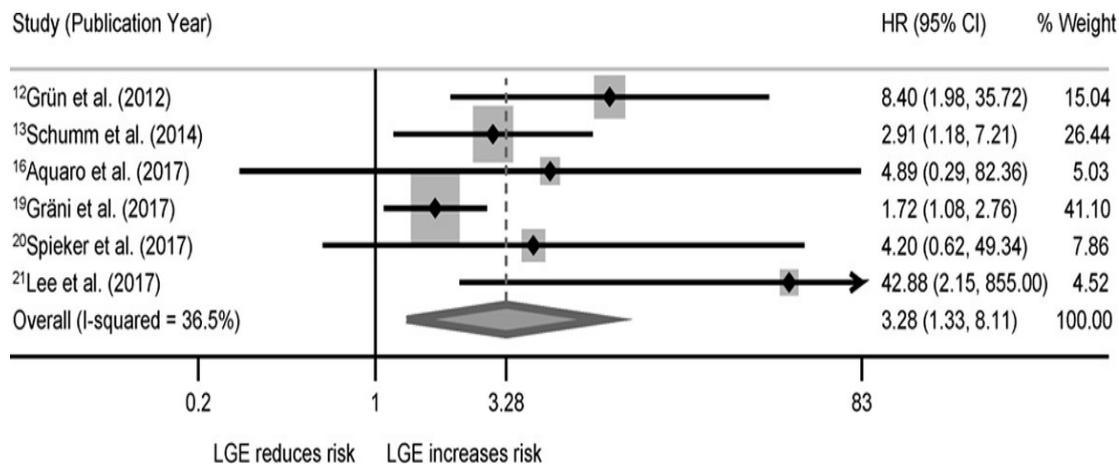## Prognostic value (longitudinal accuracy) of cardiac MRI

The scoping review identified nine studies and two systematic reviews. Most of the studies (7/9) identified in the scoping review were meta-analysed by two systematic reviews (Georgiopoulos et al. 2021 and Yang, et al 2020) that provided summary statistics for the prognostic value of cardiac MRI for predicting health outcomes.

Georgiopoulos et al. (2021) conducted a systematic review and meta-analysis of 11 articles, assessing the prognosis of 2,328 patients with acute myocarditis. Among these articles, six reported data on the presence of LGE. Overall, patients with acute myocarditis and LGE-cardiac MRI conducted early after clinical presentation (within 2 weeks from symptom onset) had a three-fold increased risk of dying or developing major cardiovascular events (MACE) during a

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[17] Applicant. (2022). RE: Application form for Application 1713.

mean 2-year follow-up, compared to those without LGE. The systematic review reported an overall incidence of mortality, life-threatening ventricular arrythmias, heart failure, and a disease recurrence rate to be 11.5% over a mean follow-up of two years.

The results of the meta-analysis, presented in Figure 1, show that presence of LGE on baseline cardiac MRI is an important independent prognostic marker that portends an increased risk of MACE.

Study (Publication Year)	HR (95% CI)	% Weight
[12]Grün et al. (2012)	8.40 (1.98, 35.72)	15.04
[13]Schumm et al. (2014)	2.91 (1.18, 7.21)	26.44
[16]Aquaro et al. (2017)	4.89 (0.29, 82.36)	5.03
[19]Gräni et al. (2017)	1.72 (1.08, 2.76)	41.10
[20]Spieker et al. (2017)	4.20 (0.62, 49.34)	7.86
[21]Lee et al. (2017)	42.88 (2.15, 855.00)	4.52
Overall (I-squared = 36.5%)	3.28 (1.33, 8.11)	100.00

LGE reduces risk   LGE increases risk

NOTE: Weights are from random-effects model

Figure 1 Pooled estimates for presence of LGE and the incidence of the combined endpoint
Source: Figure 2, p61 of Georgiopoulos et al. (2021)
CI = confidence interval; HR = hazard ratio; LGE = late gadolinium enhancement.

Yang et al. (2020) reviewed 8 articles that assessed the prognosis of 1,319 patients, comprising of both patients with clinically suspected myocarditis (44.3%) and confirmed cases of myocarditis (55.7%). The meta-analysis showed that the presence of LGE was significantly associated with an increased risk of combined outcome[18] (pooled OR, 5.85; 95% CI, 2.88 to 11.86) and MACE[19] (pooled OR, 4.57; 95% CI, 2.18 to 9.59). However, the presence of LGE was not associated with the endpoint of sudden cardiac death (SCD) or aborted SCD. In summary, the assessment group noted that the meta-analyses demonstrated the role of LGE with cardiac MRI as an important independent prognostic marker that portends an increased risk of MACE and for risk stratification and planning of follow-up for patients with myocarditis or clinically suspected myocarditis.

During the scoping review, a study was identified that followed patients similar to the population proposed in the application for a median follow-up period of 4.7 years (interquartile range [IQR]: 2.3 -7.3 years) Gräni et al 2017. The Gräni et al. (2017) study assessed 670 patients with suspected myocarditis who underwent cardiac MRI. The study reported that the presence of LGE was significantly associated with risk of MACE (HR, 2.22; 95% CI: 1.47 to 3.35) and death (HR, 1.99; 95% CI: 1.05 to 3.75). There were significant differences in the annualised rate for MACE (4.8% vs 2.1%) and death (1.7% vs 0.9%) between patients with LGE and those without LGE. Patients with LVEF <40% and LGE presence experienced markedly higher cardiac events.

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[18] Defined as MACE and requirement for extracorporeal membrane oxygenation [ECMO] or ventricular assist device [VAD]

[19] Defined as combination of all-cause death or cardiovascular death, resuscitated cardiac arrest, transplantation, appropriate ICD shock, rehospitalisation following a cardiac event and recurrent acute myocarditis.

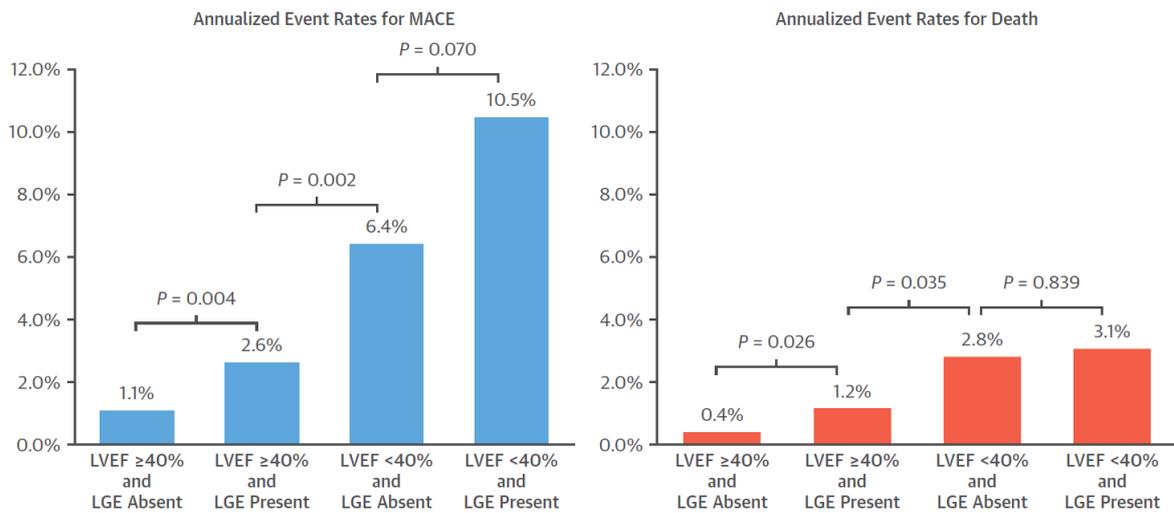Figure 2 presents the annualized event rates stratified by LGE presence and LVEF dichotomized by a 40% cutoff.

Figure 2 Annualized Event Rates Between LGE Presence and LGE Absence and LVEF in Patients with Suspected Myocarditis

Source: Figure 5, p1794 of Gräni et al. (2017)
LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MACE = major cardiovascular adverse event.

Clinical claim

The overall clinical claim made in the application was that cardiac MRI provided a more accurate diagnosis of myocarditis whilst avoiding a potentially risky invasive procedure (e.g., EMB). The assessment group considered that the claim that the use of cardiac MRI results in superior effectiveness in terms of diagnostic accuracy compared with clinical criteria/EMB was reasonable because:

- Cardiac MRI is reasonably good at diagnosing acute myocarditis as associated with high sensitivity and specificity. The meta-analysis based on the 16 individual studies of updated systematic review reported high sensitivity and specificity values and of these studies, nine studies were low risk of bias. Therefore, based on the GRADE tool, quality of evidence for diagnostic accuracy was moderate.
- LGE with cardiac MRI is an important independent prognostic marker of increased risk of MACE and is useful for risk stratification and planning of follow-up for patients with myocarditis or clinically suspected myocarditis. The quality of evidence available for the prognostic utility was moderate.

It is expected that a more accurate diagnosis for myocarditis would increase the number of patients who receive the appropriate therapy for myocarditis leading to better resolution of symptoms and a lower incidence of potential lifelong anti-atherosclerotic therapies in these incorrectly diagnosed as symptomatic CAD. However, there was no specific evidence identified in the change in management or health outcomes related to the use of cardiac MRI to diagnose acute myocarditis. Hence, evidence was uncertain.

The use of cardiac MRI results in superior safety compared with EMB in terms of less adverse events was reasonable because:

- Cardiac MRI is a non-invasive test which utilizes a non-nephrotoxic contrast agent, so its safety profile is superior to current comparators such as invasive myocardial

biopsy and invasive coronary angiography, though there were no direct comparative evidence related to the safety of cardiac MRI and these invasive comparators.

- MRI imaging is undertaken widely in Australia for other conditions and the safety profile for them is generally accepted.

The available evidence related to diagnostic accuracy, prognostic accuracy and safety are reported generally as myocarditis patients with no separate evidence relevant to Populations 1 and 2 as specified in the ratified PICO. Therefore, the clinical claim was unable to be assessed for each population separately.

13. Economic evaluation

The economic evaluation was a cost-effectiveness analysis (CEA), using a modelled cost-utility analysis (CUA) of the proposed MBS listing in the two populations of interest.

Population 1: Patients with suspected myocarditis and signs and symptoms of acute onset cardiomyopathy (acute heart failure and/or arrythmia).

Population 2: Patients with suspected myocarditis and signs and symptoms of acute coronary syndrome with an intermediate risk of obstructive coronary disease. The overall approach was to construct two separate decision models based on proposed management algorithms for the two populations, to assess the costs and benefits of cardiac MRI in diagnosing acute myocarditis.

For Population 1, cardiac MRI was not expected to improve accuracy of diagnosis or replace EMB but rather inform the prognosis based on the presence/absence of LGE, and how LGE is associated with MACE. In Population 2, cardiac MRI was expected to reduce the utilisation of CTCA with/without TTE, avoid invasive procedures such as ICA and inform long-term outcomes in the presence of LGE as described above. A summary of the economic evaluation is provided in Table 7.

Table 7   Summary of the economic evaluation

Component	Description	
	Population 1	Population 2
Perspective	Australian healthcare system	Australian healthcare system
Population	Patients with signs and symptoms of acute onset cardiomyopathy	Patients with signs and symptoms of ACS and intermediate risk of obstructive CAD
Prior testing	Blood (including troponins), ECG, CXR, TTE	Blood (including troponins), ECG, CXR, stress ECHO
Comparator	Standard management of patients with acute-onset cardiomyopathy without cardiac MRI and with/without EMB	Standard management of intermediate-risk ACS without cardiac MRI, including CTCA with/without TTE and with/without EMB
Type(s) of analysis	Cost-effectiveness analysis	Cost-effectiveness analysis
Outcomes	Incremental costs per QALY	Incremental costs per QALY
Time horizon	20 years from baseline	20 years from baseline
Computational method	Markov multi-state health transition analysis	Markov multi-state health transition analysis
Generation of the base case	Modelled. Based on the prevalence of myocarditis and the diagnostic accuracy of the proposed	Modelled. Based on the prevalence of myocarditis and the diagnostic accuracy of the proposed

Component	Description	
	Population 1	**Population 2**
	listing obtained from an updated systematic review of the literature.	listing obtained from an updated systematic review of the literature.
Health states	No MACE with pLVEF, no MACE with rLVEF, advanced HF, post-VA, post-ICD, post-heart transplant	No MACE, chronic HF, advanced HF, post-VA, post-ICD, post-heart transplant
Cycle length	Months	Months
Transition probabilities	Prevalence of myocarditis=35.1% Fibrosis in patients with myocarditis=39.0% Annualised MACE without fibrosis and pLVEF=1.1% Annualised MACE with fibrosis and pLVEF=2.6% Annualised MACE without fibrosis and rLVEF=6.4% Annualised MACE with fibrosis and rLVEF=10.5%	Prevalence of myocarditis=26.4%. Fibrosis in patients with myocarditis=48.0%% Annualised MACE rates without fibrosis=1.1% Annualised MACE rates with fibrosis=2.6%
Discount rate	5% for both costs and outcomes	5% for both costs and outcomes
Software	TreeAge Pro HealthCare 2023	TreeAge Pro HealthCare 2023

ACS = acute coronary syndrome; CAD = coronary artery disease; CXR = chest X-ray; CTCA = computed tomography guided angiogram; EMB = endomyocardial biopsy; ECG = electrocardiogram; ECHO: echocardiogram; HF = heart failure; ICA = invasive coronary angiogram; ICD = implantable cardioverter defibrillator; MACE = major adverse cardiovascular event (sudden death, hospitalisation for VA, hospitalisation for HF); MRI = magnetic resonance imaging; pLVEF = preserved left ventricular ejection fraction; QALY = quality-adjusted life year; rLVEF = reduced left ventricular ejection fraction; VA = ventricular arrythmia/tachycardia.

A time horizon of 20 years was used based on the follow up duration of Grani et al. (2017) (~14 years) and assuming that the cohort of patients who started the model in their forties may start to develop other cardiovascular diseases after 20 years due to ageing and other risk factors. However, a lifetime horizon was tested in sensitivity analysis. The model structure and health states in Population 1 was based on the MSAC guidance for analysis of investigative health technologies and is presented in Figure 3 and Figure 4, respectively.
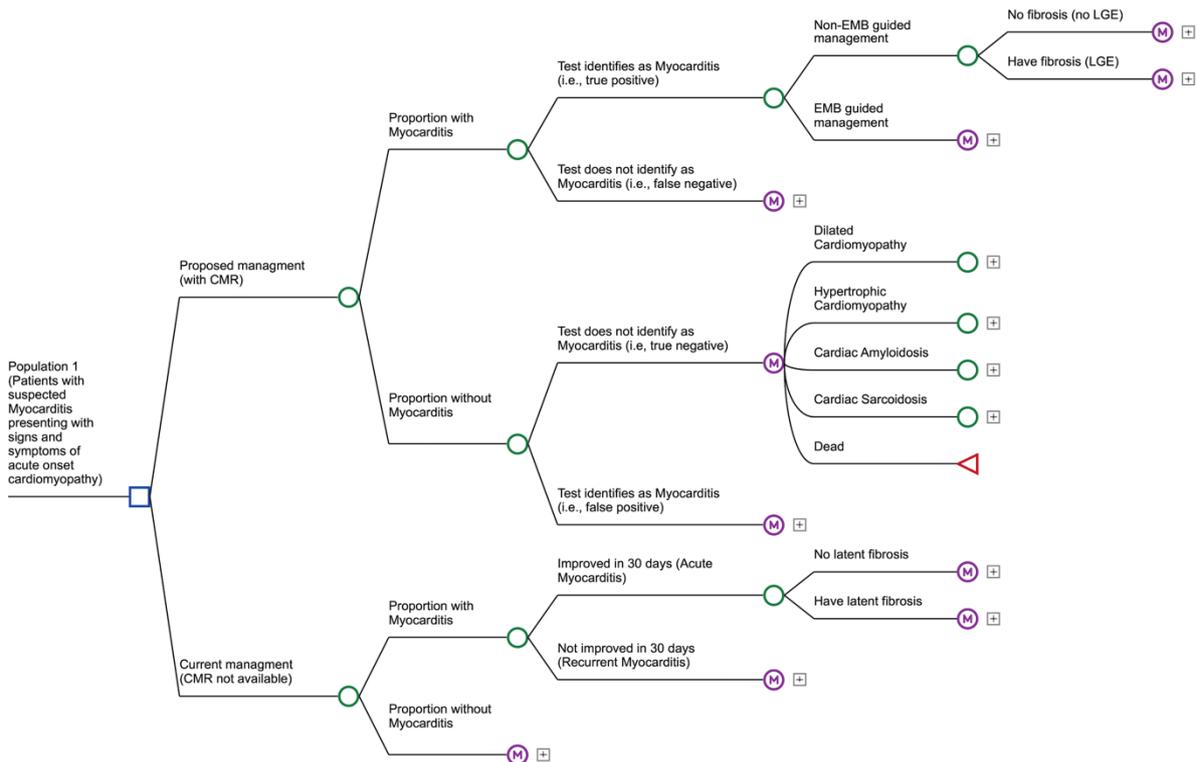
Figure 3 Structure of the economic model for Population 1

CMR = cardiovascular magnetic resonance imaging; EMB = endomyocardial biopsy; LGE = late gadolinium enhancement
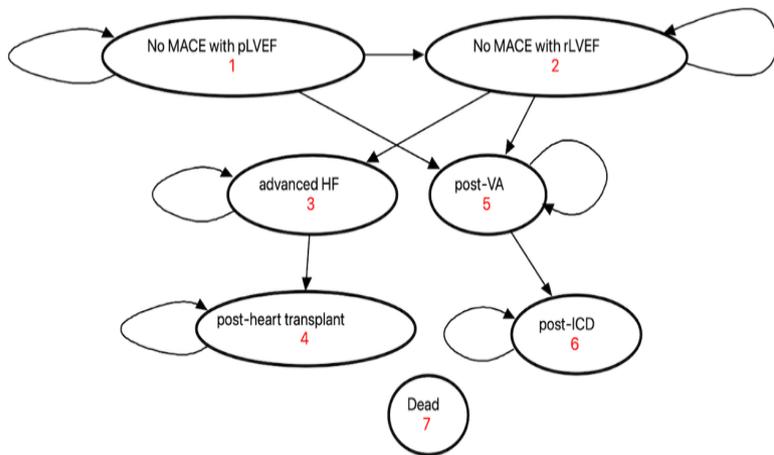

Figure 4 Health states for patients with myocarditis in Population 1

Source: Grani, C et al. 2017 and validated by Expert opinion.
ICD = implantable cardioverter defibrillator; HF = heart failure; MACE = major cardiovascular event; rLVEF = reduced left ventricular ejection fraction; VA = ventricular arrythmia.

The model structure and health states in Population 2 were based on the MSAC guidance for analysis of investigative health technologies and are presented in Figure 5 and Figure 6, respectively.
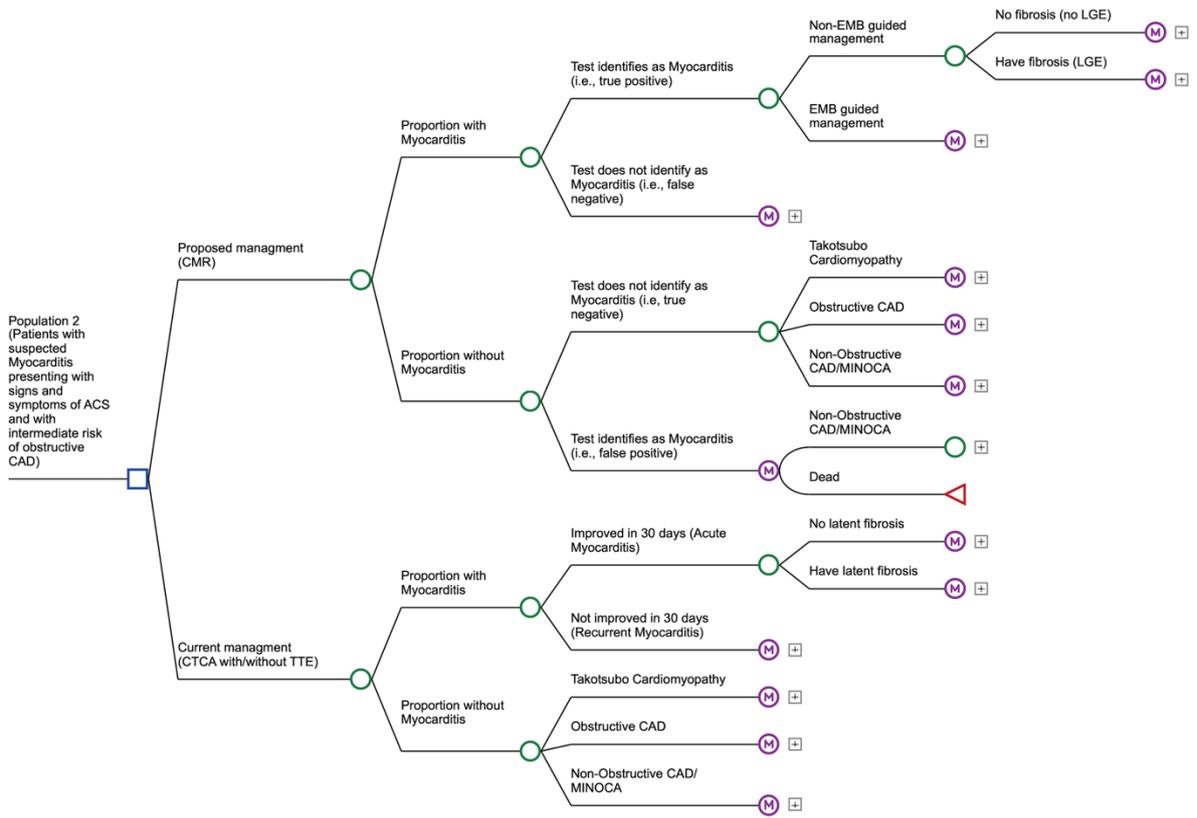
Figure 5 Structure of the economic model for Population 2

EMB = endomyocardial biopsy; CAD = coronary artery disease; CTCA = computed tomography coronary angiography; LGE = late gadolinium enhancement; MINOCA = myocardial infarction with non-obstructive coronary arteries; TTE = transthoracic echocardiogram.
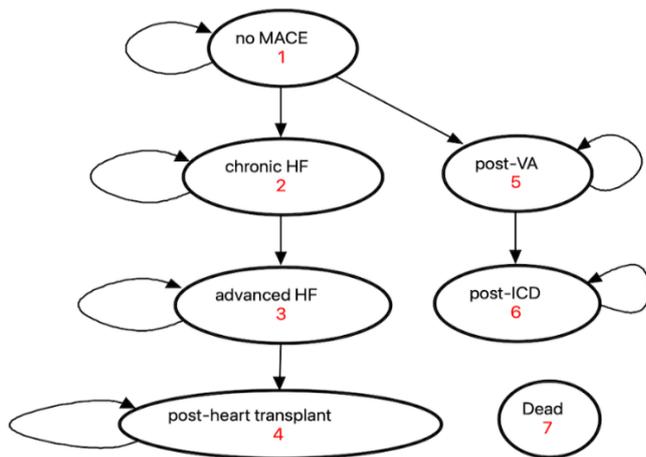

Figure 6 Health states for patients with myocarditis in Population 2

Source: Grani, C et al. 2017 and validated via Expert opinion.
ICD = implantable cardioverter defibrillator; HF = heart failure; MACE = major cardiovascular event; rLVEF = reduced left ventricular ejection fraction; VA = ventricular arrythmia.

In Population 1, the proposed listing i.e., cardiac MRI is provided to all patients and is expected to identify myocarditis with/without fibrosis via the presence or absence of LGE in their imaging results. Myocarditis patients in this population were expected to have preserved or reduced ejection fraction at presentation and have a likelihood of developing MACE, i.e., hospitalisation for heart failure, with/without ventricular arrythmias and ensuing sudden death overtime. The

25

probabilities for MACE were derived from a previous clinical trial (Grani et al. 2017) and were anticipated to be higher for patients with LGE findings. It was assumed that the benefits of identifying patients with increased risk would provide the opportunity to monitor those patients more frequently over an extended period of time, thereby resulting in an overall risk reduction of MACE. The frequency (once every 6 months) and duration of monitoring (lifetime) and the effectiveness (50% risk reduction of MACE) was based on expert opinion.

In Population 2, cardiac MRI confirms the diagnosis of myocarditis and informs prognosis for MACE. Unlike Population 1, it was anticipated that all patients in this population would have preserved ejection fraction at baseline. Patients were expected to transition to chronic heart failure, advanced heart failure, ventricular arrythmias with a possibility of sudden death. Similar to the model structure in Population 1, myocarditis patients with LGE were likely to have a higher incidence of MACE and the proposed management pathway was anticipated to reduce this risk via targeted monitoring. Patients without cardiac MRI findings of myocarditis were expected to receive investigations such as CTCA with/without TTE to rule out obstructive CAD and follow the guideline directed management for those conditions (i.e., obstructive CAD, nonobstructive CAD/ MINOCA, Takotsubo cardiomyopathy. All patients in the current management without cardiac MRI were expected to receive CTCA with/without TTE to investigate their risk of CAD. In the current management pathway, a diagnosis of myocarditis was based on the exclusion of other relevant conditions in the comparator arm. Therefore, these patients were modelled to receive no risk reduction of MACE. Further, patients without obstructive CAD in the current management pathway were expected to receive prophylactic anti-platelet therapy for at least one year in line with the NHF-CSANZ guidelines[20].

The results for the base case analysis for Population 1 are presented in Table 8.

Table 8   Base case incremental costs and effectiveness for Population 1

Parameter	Management with cardiac MRI	Standard care, no cardiac MRI	Increment
Costs	$21,955	$19,946	$2,009
QALYs	7.73	7.70	0.03
Incremental cost per QALY gained			$66,355.65

ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

The results for the base case analysis for Population 2 are presented in Table 9.

Table 9   Base case incremental costs and effectiveness for Population 2

Parameter	Management with cardiac MRI	Standard care, no cardiac MRI	Increment
Costs	$7,032	$6,258	$775
QALYs	11.54	11.49	0.05
Incremental cost per QALY gained			$15,786.91

ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

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[20] https://www.heartfoundation.org.au/Bundles/Your-heart/Conditions/fp-acs-guidelines

The sensitivity analyses informed the key drivers of the economic analysis for Population 1 and have been presented in Table 10. The potential risk reduction (RR) of a MACE with monitoring in patients with LGE and the time horizon for the model were the major drivers of cost-effectiveness in Population 1. A RR of 0.31 for MACE was required to bring the ICER below $50,000/QALY.

Table 10 Key drivers of the model in Population 1

Description	Method/Value	Impact Base case: $66,356 QALY gained
Time horizon	A time horizon of 20 years was used in the base-case analysis as the trial (Grani et al., 2017) for modelling the outcomes followed patients for 14 years.	*High, favours cardiac MRI* *Using a lifetime horizon (i.e., until 85 years of age) reduced the ICER to $27,737/QALY.*
Risk reduction in MACE after monitoring myocarditis patients with LGE and pLVEF	Data about this parameter was not available in the literature and a potential risk reduction of 50% was obtained via Expert opinion. The sensitivity analysis explored the results over a range of 25-75%.	*High, favours the comparator* *Using a risk reduction of 25% increased the ICER to $114,544/QALY*
Probability of MACE in myocarditis patients with LGE and pLVEF	The probability of this outcome was obtained from a previous clinical trial (Grani et al., 2017).	*Moderate, favours the comparator* *A 10% decrease in this parameter increased the ICER to $78,859/QALY gained.*
Cost of cardiac MRI	The cost of this item was assumed based on a previous MBS listing for cardiac MRI for mRNA vaccine related myocarditis.	*Moderate, favours cardiac MRI* *A 25% decrease in this parameter decreased the ICER to $58,495/QALY gained.*

ICER = incremental cost-effectiveness ratio; LGE = late gadolinium enhancement; MACE = major adverse cardiovascular event; MRI = magnetic resonance imaging; pLVEF = preserved left ventricular ejection fraction; QALY = quality-adjusted life year.

The key drivers of the economic analysis for Population 2 are presented in Table 11. The potential risk reduction (RR) of a MACE with monitoring in patients with LGE, probability of a MACE in myocarditis patients with LGE and cost of cardiac MRI and the cost of prophylactic ACS medications were the major drivers of cost-effectiveness in Population 2.

Table 11 Key drivers of the model in Population 2

Description	Method/Value	Impact Base case: $15,787/QALY gained
Time horizon	A time horizon of 20 years was used in the base-case analysis as the trial (Grani et al., 2017) for modelling the outcomes followed patients for 14 years	*High, favours cardiac MRI* *Using a lifetime horizon reduced the ICER to $8,261/QALY.*
Risk reduction in MACE after monitoring myocarditis patients with LGE	Data about this parameter was not available in the literature and a potential risk reduction of 50% was obtained via Expert opinion. The sensitivity analysis explored the results over a range of 25-75%.	*High, favours the comparator* *Using a risk reduction of 25% increased the ICER to $32,745/QALY gained.*
Probability of MACE in myocarditis patients with LGE	The probability of this outcome was obtained from a previous clinical trial (Grani et al., 2017)	*Moderate, favours the comparator* *A 10% decrease in this parameter increased the ICER to $19,921/QALY gained.*
Cost of cardiac MRI	The cost of this item was assumed based on a previous MBS listing for cardiac MRI for mRNA vaccine related myocarditis	*Moderate, favours the comparator*

Description	Method/Value	Impact Base case: $15,787/QALY gained
		A 25% increase in this parameter increased the ICER to $20,639/QALY gained.
Cost of prophylactic ACS medications	Based on NHF and CSANZ guidelines, a course of prophylactic ACS medications was assumed for all ACS patients without a diagnosis of myocarditis in both the proposed and current management pathways	*Moderate, favours the comparator* *A 25% decrease in this parameter increased the ICER to $19,410/QALY gained.*

ACS: Acute Coronary Syndrome; CSANZ = Cardiac Society of Australia and New Zealand; ICER = incremental cost-effectiveness ratio; LGE = late gadolinium enhancement; MACE = major adverse cardiovascular event; MRI = magnetic resonance imaging; NHF = National Heart Foundation; QALY = quality-adjusted life year.

The sensitivity analyses for cost-effectiveness of cardiac MRI in population 1 and population 2 have been presented in Table 12 and Table 13.

Table 12 Sensitivity analyses for Population 1

Analysis	Incremental cost	Incremental QALY	ICER	% change from base case analysis
Base case	$2,009	0.03	$66,355.65	-
Time horizon, lifetime i.e., until 85 years of age (20 years was used in base case)	$2,568	0.09	$27,737.46	-58%
Time horizon, 10 years (20 years was used in base case)	$1,559	0.007	$209,912.05	+216%
Time horizon, 5 years (20 years was used in base case)	$1,279	0.002	$705,970.39	+964%
Discount rate 0%	$2,050	0.03	$64,032.62	-4%
Discount rate 3.5%	$2,021	0.03	$65,649.12	-1%
RR of MACE with monitoring and prophylactic treatment of those with LGE and pLVEF, 0.75	$2,043	0.02	$114,544.18	+73%
RR of MACE with monitoring and prophylactic treatment of those with LGE and pLVEF, 0.25	$1,974	0.04	$45,658.24	-31%
Probability of MACE in those with LGE and pLVEF, +10%	$1,972	0.03	$57,327.97	-14%
Probability of MACE in those with LGE and pLVEF, -10%	$2,048	0.03	$78,858.75	+19%
Cost of cardiac MRI, +25%	$2,247	0.03	$74,216.53	+12%
Cost of cardiac MRI, -25%	$1,771	0.03	$58,494.77	-12%

RR = relative risk; MACE = major adverse cardiovascular event; LGE = late gadolinium enhancement; pLVEF = preserved left ventricular ejection fraction; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table 13 Sensitivity analyses for Population 2

Description	Incremental cost	Incremental QALY	ICER	% change from base case analysis
Base case	$775	0.05	$15,786.91	-
Time horizon, lifetime i.e., 85 years of age (20 years was used in base case)	$1,237	0.15	$5,770.88	-48%
Time horizon, 10 years (20 years was used in base case)	$419	0.01	$37,129.97	+135%
Time horizon, 5 years (20 years was used in base case)	$202	0.002	$84,549.82	+436%
Discount rate 0%	$805	0.05	$15,510.70	-2%
Discount rate 3.5%	$783	0.05	$15,703.18	-1%
RR of MACE with monitoring and prophylactic treatment of those with LGE and pLVEF, 0.75	$821	0.03	$32,744.77	+107%
RR of MACE with monitoring and prophylactic treatment of those with LGE and pLVEF, 0.25	$726	0.07	$9,800.94	-38%
Probability of MACE in those with LGE and pLVEF, -10%	$816	0.04	$19,920.91	+26%
Probability of MACE in those with LGE and pLVEF, +10%	$735	0.06	$12,941.59	-18%
Cost of cardiac MRI, +25%	$1,013	0.05	$20,638.61	+31%
Cost of cardiac MRI, -25%	$536	0.05	$10,935.20	-31%
Cost of prophylactic ACS medication-25%	$952	0.05	$19,410.07	+23%

RR = relative risk; MACE = major adverse cardiovascular event; LGE = late gadolinium enhancement; pLVEF = preserved left ventricular ejection fraction; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Additionally, several alternate scenarios for the cost-effectiveness of cardiac MRI were explored in population 2.

Assuming 50% uptake of cardiac MRI (based on expert opinion) the ICER remained unchanged ($15,787/QALY gained). The reduction in costs was accompanied by a simultaneous reduction in QALYs. In Population 2, if cardiac MRI was performed as a second line investigation after ruling out obstructive CAD using CTCA with/without TTE, the ICER was $21,426/QALY.

In conclusion, the management pathway with cardiac MRI resulted in an ICER of $66,356/QALY in population 1. The assessment group considered that these findings may have been primarily driven by the absence of a comparable investigative health technology to contrast the increased cost of cardiac MRI for the diagnosis or exclusion of myocarditis in the current management pathway.

In population 2, the management pathway with cardiac MRI resulted in an ICER of $15,787/QALY gained. The assessment group considered improved value for money of cardiac MRI in population 2 may be driven by the prognostic value of cardiac MRI in highlighting patients with fibrosis via the presence of LGE and the potential risk reduction of a downstream MACE in these patients with monitoring. The avoidable costs of placing potential myocarditis patients on prophylactic ACS medications was another factor that contributed to the cost-effectiveness of cardiac MRI in this population. Further, compared to Population 1, a higher proportion of patients in Population 2 had LGE in their cardiac MRI findings (Population 1: 39%, Population 2: 48%).

14. Financial/budgetary impacts

An epidemiological approach was used to estimate the expected extent of usage and the financial implications of listing cardiac MRI on the MBS. This approach was chosen instead of a market-based approach because the MBS items for the comparator tests (e.g., EMB, CTCA, or TTE) are not restricted to the proposed population.

The net financial implications to the MBS for both Population 1 and 2 resulting from the proposed listing of cardiac MRI are summarised in Table 14.

Table 14 Net financial implications of cardiac MRI to the MBS

Parameter	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Year 4 (2027)	Year 5 (2028)	Year 6 (2029)
Population 1						
Estimated use and cost of the proposed health technology						
Number of people eligible for cardiac MRI	8,710	8,839	8,966	9,091	9,214	9,337
Number of people who receive cardiac MRI	4,355	4,420	4,483	4,545	4,607	4,669
Cost to the MBS	$3,685,782	$3,740,374	$3,794,116	$3,846,726	$3,899,060	$3,951,052
Change in use and cost of other health technologies						
Change in use of EMB	0	0	0	0	0	0
Net change in costs to the MBS	$0	$0	$0	$0	$0	$0
Net financial impact to the MBS (Population 1)	**$3,685,782**	**$3,740,374**	**$3,794,116**	**$3,846,726**	**$3,899,060**	**$3,951,052**
Population 2						
Estimated use and cost of the proposed health technology						
Number of people eligible for cardiac MRI	34,841	35,357	35,865	36,363	36,857	37,349
Number of people who receive cardiac MRI	17,421	17,679	17,933	18,181	18,429	18,674
Cost to the MBS	$14,743,127	$14,961,496	$15,176,463	$15,386,905	$15,596,240	$15,804,206
Change in use and cost of other health technologies						
Change in use of CTCA	-17,421	-17,679	-17,933	-18,181	-18,429	-18,674
Change in use of TTE	-8,710	-8,839	-8,966	-9,091	-9,214	-9,337
Change in use of EMB	0	0	0	0	0	0
Net change in costs to the MBS	-$13,341,633	-$13,539,243	-$13,733,776	-$13,924,212	-$14,113,648	-$14,301,845
Net financial impact to the MBS (Population 2)	**$1,401,494**	**$1,422,253**	**$1,442,688**	**$1,462,692**	**$1,482,592**	**$1,502,361**
Total net financial impact to the MBS (Population 1 and 2)	**$5,087,276**	**$5,162,627**	**$5,236,803**	**$5,309,418**	**$5,381,652**	**$5,453,413**

EMB = endomyocardial biopsy; CTCA = computed tomography coronary angiography, EMB = endomyocardial biopsy, MBS = Medicare Benefits Schedule, TTE = transthoracic echocardiogram.

Estimations of the extent of use and financial implications of cardiac MRI were highly uncertain due to numerous assumptions that were required to estimate the financial impact. For example, in estimating the financial impact, it was assumed that 50% of CTCA±TTE procedures would be avoided due to the listing of cardiac MRI in Population 2. However, based on feedback from a clinical expert, majority of patients presenting with signs and symptoms of ACS undergo CTCA±TTE to rule out CAD before undergoing cardiac MRI testing. As a result, the use of CTCA±TTE may have been underestimated, which likely underestimated the financial impact of listing cardiac MRI. Furthermore, the financial estimates were also sensitive to incidence of myocarditis, proportion of patients in Population 1 and 2, and uptake rate of cardiac MRI.

15. Other relevant information

Nil

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- Temporary Medicare Benefits Schedule (MBS) item 63399 for cardiac MRI for mRNA-associated myocarditis is due to cease in December 2024. This application will inform whether this service should continue for eligible patients. MSAC will need to consider how patients can access a cardiac MRI, which may assist with accessing the COVID-19 vaccine claims scheme, noting that usage of MBS item 63399 is in decline.

- The proposed item descriptor did not include patients with suspected myocarditis who have a low risk of obstructive coronary artery disease (CAD). This means the proposed item would result in a service gap for some patients currently able to access this service under MBS Item 63399. MSAC may want to consider cardiac MRI in all patients suspected of having myocarditis regardless of cause.

- The evidence supported that cardiac MRI had high sensitivity and specificity in diagnosing myocarditis compared to endomyocardial biopsy (EMB) and it likely also had superior safety, but there was no evidence that cardiac MRI changed health outcomes or management.

- There may be additional clinical utility that was not captured in the assessment, in identifying patients with myocarditis-pericarditis.

- Population 2 was very broad and the risk of leakage seems likely. Patients that have had a cardiac MRI will still always undergo coronary imaging to rule out obstruction, so it will be an adjunct rather than a replacement. Cardiac MRI was positioned before coronary imaging in the clinical algorithm, which was not congruent with the wording of the item descriptor. Proposing cardiac MRI as a replacement rather than adjunct to coronary imaging for population 2 does not reflect clinical practice and will also have implications for the economics.

- The proposed MBS item descriptor and fee were consistent with temporary MBS item 63399, however the appropriate fee may be lower than this, because it is a less resource-intensive MRI procedure than other current cardiomyopathy MRI procedures, and lowering the fee would bring this item in line with comparable cardiac MRI MBS items.

Economic issues:

- In the absence of published evidence on the change in management following detection of late gadolinium enhancement (LGE) changes and the relative effectiveness of regular

monitoring compared to standard of care, expert opinion was used to inform some key model inputs. Reliance on expert opinion made the outcomes highly uncertain.

Financial issues:

- There were a lack of prevalence and incidence data for myocarditis in Australia; therefore, the applicability of the estimated utilisation was uncertain as it was based on international sources.

- The financial estimates were highly uncertain, and likely under-estimated. The assumption that 50% of computed tomography coronary angiography (CTCA) ± transthoracic echocardiogram (TTE)procedures would be avoided due to the listing of cardiac MRI for population 2 may not be realised in clinical practice. This assumption also had a major impact on the ICER.

- The financial estimates were sensitive to the incidence of myocarditis, proportion of patients in population 1 vs 2, and the uptake rate of cardiac MRI, all of which were uncertain.

Other relevant issues:

- The applicant proposed the service be performed by CSANZ-certified specialists. However, this would limit patient access, and no restriction (in terms of certification) should be considered for consistency with MBS-listed MRI services.

ESC discussion

ESC noted that this application from the Cardiac Society of Australia and New Zealand (CSANZ) requested Medicare Benefits Schedule (MBS) listing of cardiac magnetic resonance imaging (MRI) for the diagnosis of myocarditis. ESC noted that MSAC has not previously considered cardiac MRI for the diagnosis of myocarditis. However, ESC noted that in April 2017, MSAC considered *Application 1432 – Cardiac MRI of patients with suspected non-ischaemic cardiomyopathy (Part B)*. Population 5 of Application 1432 included patients with cardiomyopathies due to acute coronary syndrome (ACS), myocarditis or Takotsubo cardiomyopathy (TTC). At the time MSAC did not support population 5 as the cost-effectiveness analysis (CEA) was highly uncertain due to limited evidence on long term health outcomes. MSAC advised a more comprehensive CEA with more inputs and a longer time horizon was required. ESC noted that during the COVID-19 pandemic, on 6 December 2021 the MSAC Executive supported a temporary cardiac MRI MBS item for suspected mRNA COVID-19 vaccine-associated myocarditis (MBS item 63399) at a fee of $904.70, and the MSAC Executive then supported extending the temporary item on 19 August 2022, pending the consideration of this application.

ESC noted myocarditis is inflammation of the heart muscle (myocardium) characterised by presence of inflammatory infiltrate, degenerative and necrotic changes to cardiomyocytes. ESC noted although the aetiology of myocarditis remains unknown in ~50% of cases, it can be caused by viral infections, drugs, environmental factors and autoimmune diseases. The diagnosis of myocarditis is challenging as patient presentation ranges from being asymptomatic to presenting with subtle cardiogenic shock to sudden death. The symptoms include a sudden onset of acute chest pain, dyspnoea, persistent or intermittent palpitations within <1 month of symptom onset and diagnosis. ESC noted that the investigation results of electrocardiogram (ECG), echocardiogram, cardiac markers in patients with myocarditis are abnormal and the condition often mimics acute coronary syndrome (ACS).

ESC noted that cardiac MRI is a non-invasive imaging technique that can evaluate both the structure and function of the heart without the use of ionising radiation. Cardiac MRI is MBS-listed for other indications: congenital heart disease (MBS item 63385, fee $473.90), aortic disease (MBS item 63391, fee $426.50), arrhythmogenic right ventricular cardiomyopathy (MBS items 63395 and 63397, fee $904.70) and cardiac mass (MBS item 63388, fee $473.90).

ESC noted that the current gold standard for diagnosing myocarditis is through endomyocardial biopsy (EMB) that can assess the severity of fibrosis in the heart, enable immunohistochemical analysis and help detect viruses via polymerase chain reaction (PCR). However, EMB is a technically challenging procedure that is only performed in specialist centres, resulting in access issues for some patients. Therefore, many patients are typically diagnosed with clinically suspected myocarditis based on symptoms, signs and other cardiac tests. However, other cardiac conditions can present similarly to myocarditis, which makes ascertaining, or excluding, a specific diagnosis challenging.

ESC noted that there were no Australian prevalence nor incidence data for myocarditis. The applicant estimated the overall incidence was 30 cases per 100,000-person years, with ~7,900 cases per year in Australia. ESC considered the size of the population eligible for testing remained uncertain, due to the uncertain applicability of the international evidence.

ESC noted and welcomed consultation inputs from six (6) professional organisations, two (2) consumer organisations and seven (7) individuals, of which six (6) were specialists and one (1) a family member of a consumer.

ESC noted support for the application from consumers, specialists and cardiac organisations, with consultation input pointing to the benefits of cardiac MRI over biopsy and improved access for patients. ESC noted specialist comment about the potential additional non-health value of the test for early accurate diagnosis of myocarditis in people such as heavy vehicle drivers and pilots who may need to have restrictions put in place, or whose ability to work may hinge on their diagnosis. The Australian Society of Medical Imaging and Radiation Therapy (ASMIRT) expressed some concern regarding the applicant's recommendation that delivery of the proposed service be restricted to certified clinicians. Currently the certification requires an external examination to be completed and this exam is not currently conducted in Australia. However, ESC noted the proposed certification requirement is not in other cardiac MRI applications or approved MBS items. ESC considered that including it here would limit patient access, and recommended it not be added. ESC noted that consumer concern may arise if an item to assess mRNA COVID-19 vaccine related complications is not available on the MBS.

ESC noted the application proposed two populations:

- Population 1 – patients with signs and symptoms of acute onset cardiomyopathy (acute heart failure and/or arrythmia) suggestive of acute myocarditis.

- Population 2 – patients presenting with signs and symptoms of acute coronary syndrome (ACS) with an intermediate risk of obstructive coronary artery disease (CAD), or suspected myocarditis.

ESC noted that the first-line investigations for population 1 currently include chest X-ray, ECG, echocardiogram, cardiac biomarker measurements and can include cardiac MRI. EMB is a second-line investigation. ESC noted that EMB is clinically recommended and may be favoured over cardiac MRI for some cases, but that some patients cannot undergo EMB due to complex anatomy. ESC also noted the applicant's claim that about 50% of patients will undergo a cardiac MRI if EMB results are non-specific. ESC considered the risk of leakage for population 1 was high, as almost all patients with heart failure have myocarditis as a differential diagnosis for their heart failure and/or arrythmia.

ESC noted that, for population 2, myocarditis can mimic ACS, as in both cases patients can have abnormal ECG and cardiac biomarker levels. ESC noted the majority of patients presenting with ACS will receive a coronary angiogram or coronary computed tomography (CT) scan. ESC noted that some patients will receive treatment for ACS with anti-platelet therapies when they really have undiagnosed myocarditis. ESC agreed with PASC that population 2 was broad due to the various aetiologies, making it difficult to characterise, and thus considered there was a high risk

of leakage for cardiac MRI in population 2. ESC noted PASC had suggested including pre-test probabilities of CAD as described in National Heart foundation (NHF)-CSANZ guidelines to identify population that would benefit from the test, and that the DCAR had added this to the practice note. ESC noted PASC had also suggested limiting the test to patients who do not improve after a certain time (i.e. chronic ACS) or have high troponin levels. ESC noted the applicant's argument that MRI is useful in the acute setting and that troponin laboratory tests are variable but unreliable.

ESC noted the temporary MBS item 63399 for cardiac MRI for suspected mRNA-associated myocarditis, was due to end on 31 December 2024. ESC noted other patient populations such as young adults, and those with cancer immunotherapy-related myocarditis, would not be covered by the testing proposed in this application as they will be considered to have "low risk coronary artery disease (CAD)". ESC considered this means that after December 2024, some patients currently covered by MBS item 63399 will no longer have access to this service. ESC noted that in the pre-ESC response, the applicant stated that such patients would qualify for the service if they had previous abnormal cardiac test results, which ESC disagreed with. ESC considered that young adults or cancer immunotherapy related myocarditis may not have signs or symptoms of cardiomyopathy (population 1) and the population 2 item descriptor clearly is intended for 'intermediate risk CAD' patients.

ESC forewarned the ending of temporary MBS item 63399 ending in December 2024 may deprive patients of a service that may assist in accessing the COVID-19 vaccine claims scheme, although these patients may potentially be able to receive an MRI in the public system, and ESC also noted that usage of MBS item 63399 is in decline. To address the loss of access for some patients after the current temporary item ends and lack of coverage for patients with suspected myocarditis with 'low risk CAD', ESC queried whether the item proposed under this application should expand the eligible population to all patients with suspected myocarditis, regardless of cause. ESC considered MSAC should consider the gap in coverage if this is not supported, and to what extent the gap is clinically relevant.

ESC noted the single proposed MBS item descriptor covered both proposed populations and was based on the temporary item descriptor (MBS item 63399). ESC noted the proposed fee of $904.70 was also the same as fee for the temporary MBS item (and a small extra fee was also included where gadolinium contrast is used). However, ESC also noted that most other cardiac MRIs attract lower MBS fees: around $400 to $500. ESC considered that a fee around $900 was relatively high compared to the likely time 'on magnet' for this service in its experience, although the resources required for a cardiac MRI can also vary between patients. ESC considered that funding medical services related to COVID-19 had been a matter of urgency during the pandemic. Overall, ESC considered the higher fee for the COVID-related MRI item did not accurately reflect the resources required for this service nor the appropriate relativity to other cardiac MRI items, and proposed that a more appropriate fee would be more closely aligned with the fees for the other cardiac MRI MBS items.

ESC noted the clinical management algorithms. ESC noted for population 1, current management is that patients presenting with signs and symptoms of acute onset of heart failure with or without arrythmia undergo standard investigations and if they do not improve, they go onto have EMB for a definitive diagnosis. In the proposed clinical management pathway, patients with clinically suspected myocarditis who are haemodynamically stable would receive cardiac MRI. In instances where patient does not improve or a histological diagnosis is required to guide treatment, EMB will still be performed. ESC noted the applicant's claim that with cardiac MRI, 80% of patients can avoid an invasive EMB. ESC considered that in its experience, in real-world clinical practice very few people with myocarditis end up receiving an EMB test, and the clinical decision is often to make a diagnosis without an EMB. ESC therefore considered that assuming

such high uptake of EMB in the comparator for population 1 was likely inappropriate. ESC suggested evidence on the proportion of patients in population 1 who would actually receive an EMB test (as this is based on clinical discretion) under current testing would be helpful to inform more accurate estimates of the cost-effectiveness and cost.

ESC noted that in the current algorithm for the 'ACS mimic' population 2, high-risk unstable patients undergo invasive coronary angiography (ICA) following standard investigations. If patient is stable and have intermediate risk of CAD, they receive computed tomography coronary angiography (CTCA) ± transthoracic echocardiogram (TTE). ESC noted in this population only patients with unconfirmed obstructive CAD and suspected myocarditis would receive an EMB. ESC noted in the proposed algorithm, when obstructive CAD cannot be confirmed, cardiac MRI would be used to diagnose myocarditis. ESC agreed with PASC's concerns that cardiac MRI would be introduced earlier than proposed as a triage test before obstructive CAD is excluded. ESC also noted the applicant's claim that myocarditis is the most likely diagnosis for population 2 patients, and that cardiac MRI would reduce the number of patients requiring coronary imaging and thus exposure to ionising radiation. However, ESC considered that in real-world practice, cardiac MRI would always be performed in addition to (rather than replacing) angiography in patients with an intermediate risk of ACS – therefore the replacement of imaging would be zero in population 2. ESC considered the positioning of cardiac MRI in the clinical management algorithm before coronary angiogram or cardiac CT was at odds with the wording in the proposed item descriptor stating "... the purpose of cardiac MRI in this population is to diagnose myocarditis and not to rule out CAD". Thus, ESC questioned the appropriate clinical place of cardiac MRI for population 2.

ESC noted that the clinical evidence underpinning the clinical effectiveness and safety claims was from a systematic review and meta-analyses of cardiac MRI for diagnosis of myocarditis, including either diagnosis via EMB or clinical suspected myocarditis. ESC noted there was no direct test-to-health outcomes evidence available for cardiac MRI for diagnosis of acute myocarditis. ESC noted that populations 1 and 2 could not be disaggregated in the evidence, and that a linked evidence approach was used.

ESC noted that three clinical aspects of cardiac MRI were addressed in the DCAR:

- relative safety of performing cardiac MRI

- diagnostic accuracy of cardiac MRI compared with EMB/clinical criteria

- prognostic value (longitudinal accuracy) of cardiac MRI in patients with suspected or acute myocarditis, clinical utility of the investigative medical service in terms of impact on patient management, and the impact on health outcomes.

ESC noted that there was no direct evidence to assess comparative safety, so general safety data for cardiac MRI (with gadolinium contrast) were used. ESC noted the advantages of cardiac MRI include a good safety profile without exposure to ionising radiation (lower risk of long-term radiation-induced cancer) and limited nephrotoxicity risk; potential harms and disadvantages include its inability to be used in patients with medical devices (pacemakers) or suffering from claustrophobia, and gadolinium use has a rare risk of acute allergy (in 0.07% of patients) and may cause nephrogenic fibrosis. Overall ESC considered superior safety was likely reasonable.

Regarding accuracy and test performance, ESC noted that the included five studies were systematic reviews and meta-analyses (n = 7,522) that had a high risk of bias. Sixteen individual studies were also included (n = 1,246), nine of which were assessed to have a low risk of bias. Four cardiac MRI sequences (index tests) were considered: T1 mapping, T2 mapping, late gadolinium enhancement (LGE) and Lake Louise Criteria (LLC). The systematic review revealed that, for each index test, cardiac MRI demonstrated high sensitivity and high specificity, and a

positive likelihood ratio of >5 and a negative likelihood ratio of <1. ESC considered that in the combined analysis, cardiac MRI showed higher sensitivity and specificity than EMB for each of the four MRI sequences.

For prognostic value, ESC noted that the included two studies were systematic reviews and meta-analyses (n = 3,647) that had a moderate risk of bias. Nine individual studies were also included (n = 2,139), two of which were included in the systematic review. ESC noted that detection of LGE was the strongest independent predictor of clinical outcomes: patients with LGE had three times increased risk of dying or developing major adverse cardiovascular events (MACE) during a mean 2-year follow-up compared to patients with no LGE on their cardiac MRI[21].

However, ESC noted that no evidence was available to assess change in management or health outcomes using cardiac MRI in patients with acute myocarditis. ESC noted linked evidence showed that:

- for population 1, although MRI findings can help stratify risk, there were no clear guidelines on how myocarditis patients should be monitored or managed.

- for population 2, cardiac MRI can reduce the use of coronary CT (to rule out CAD) by confirming diagnosis of myocarditis through exclusion, and it can allow avoiding unnecessary medications (anti-platelet therapy). However, ESC considered this to be highly uncertain due to the low-quality evidence presented.

Overall, ESC considered that cardiac MRI was likely superior in terms of diagnostic accuracy and prognosis compared with clinical criteria and EMB, but there was no evidence of change in management or improved health outcomes. ESC considered that a claim of non-inferior effectiveness may be more appropriate.

ESC agreed with PASC that a diagnosis of myocarditis had value of knowing, with the main benefit being to enable diagnosed patients to resume or avoid exercise. However, ESC considered the potential value of knowing was uncertain as there was no evidence or guideline-directed management for those patients in whom cardiac MRI detects LGE changes.

ESC noted that the economic evaluation included separately modelling each population and that for both populations the model was a CEA using a Markov multi-state health transition analysis with a time horizon of 20 years. ESC noted that the analyses used decision trees that attempted to mimic the placement of MRI in the proposed clinical management algorithms: ESC considered this was reasonable for population 1, but uncertain for population 2. ESC considered the models were overall structurally sound, however the results were highly uncertain due to low quality inputs.

For population 1, ESC noted that the model was structured so that cardiac MRI is provided to all patients and is expected to identify myocarditis with or without fibrosis via the presence or absence of LGE in their imaging results. Myocarditis patients in this population were expected to have preserved or reduced left ventricular ejection fraction (LVEF) at presentation and a likelihood of developing MACE (hospitalisation for heart failure, with or without ventricular arrythmias and ensuing sudden death over time). ESC noted that the probabilities of MACE (derived from a previous clinical trial)[22] were anticipated to be higher for patients with LGE findings. The model assumed that identifying patients with increased risk would provide the

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[21] Georgiopoulos, et al (2021). Prognostic Impact of Late Gadolinium Enhancement by Cardiovascular Magnetic Resonance in Myocarditis. *Circ Cardiovasc Imaging*, 14(1), e011492. https://doi.org/doi:10.1161/CIRCIMAGING.120.011492

[22] Gräni, C., et al. (2017). Prognostic Value of Cardiac Magnetic Resonance Tissue Characterization in Risk Stratifying Patients With Suspected Myocarditis. *J Am Coll Cardiol*, 70(16), 1964-1976.

opportunity to monitor those patients more frequently over an extended period of time, and result in an overall risk reduction of MACE.

ESC considered that while the DCAR had populated the model with the best available data, some of the key inputs were of low-quality and therefore highly uncertain as they were based on expert opinion: these were frequency (once every 6 months) and duration of monitoring (lifetime), and the effectiveness of monitoring (50% risk reduction of MACE). ESC considered there were multiple issues that affected the economic evaluation, some of which also affected the financial estimates:

- The analysis used international estimates of incidence and prevalence, as no Australian estimates were available. Other input parameters were derived from relevant studies, and where data were unavailable (e.g. changes in management with LGE, the relative effectiveness of regular monitoring compared to standard care, uptake of cardiac MRI), then inputs were sourced from expert opinion.

- Very few people with myocarditis receive an EMB in current clinical practice. ESC considered that information on this proportion if available would be informative for MSAC decision-making.

- It was assumed based on expert opinion that 50% of CTCA±TTE procedures would be avoided due to the listing of cardiac MRI in population 2. However, in its experience ESC considered most patients presenting with signs and symptoms of ACS undergo CTCA±TTE to rule out CAD before undergoing cardiac MRI testing. ESC considered this cost-offset from CTCA+/-TTE avoided was unlikely to be realised in practice, and that this will have substantially affected the economic and financial analyses.

- A 20-year time horizon was used to reflect the follow-up time in Grani et al. (2017), but ESC considered it likely that after 20 years patients may develop other cardiovascular diseases due to risk factors such as ageing.

- Age-specific utilities of patients with preserved LVEF were assumed to be similar to the general population of Australia and were derived from the study by Clemens et al. (2014)[23], and patients with reduced LVEF were assumed to have the health utility associated with chronic heart failure.

ESC noted the incremental cost-effectiveness ratio (ICER) for population 1 was reported at $66,356 per quality-adjusted life year (QALY), however ESC considered this result to be extremely uncertain due to the reliance on expert opinion. ESC noted that the key drivers of the ICER for population 1 were time horizon, risk reduction of MACE, probability of MACE, and the cost of cardiac MRI. ESC considered that the ICER for population 1 was primarily driven by the absence of a comparable investigative health technology to contrast the increased cost of cardiac MRI for the diagnosis or exclusion of myocarditis in the current management pathway.

For population 2, ESC noted that the model was structured so that cardiac MRI confirms a myocarditis diagnosis and informs prognosis for MACE. The model assumed that all patients in this population have preserved ejection fraction at baseline (unlike population 1), and that patients transition to chronic heart failure, advanced heart failure or ventricular arrythmias, with a possibility of sudden death. The model also assumed myocarditis patients who have LGE are likely to have a higher incidence of MACE, and the proposed management pathway reduced this risk via targeted monitoring.

ESC also noted the model was structured so that patients who are not diagnosed with myocarditis through cardiac MRI will go on to CTCA±TTE to rule out obstructive CAD, and that

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[23] Clemens, S., et al. (2014). A comparison of EQ-5D-3L population norms in Queensland, Australia, estimated using utility value sets from Australia, the UK and USA. *Qual Life Res*, *23*(8), 2375-2381.

management guidelines will be followed for those conditions. Also, the model assumed that currently all patients will undergo CTCA±TTE to investigate their risk of CAD. ESC recalled that the application's claim was that cardiac MRI will reduce the proportion of patients receiving CTCA±TTE, but considered this may not be realised in real-world practice and led to an overestimation of the cost offsets.

ESC noted that in the comparator arm a diagnosis of myocarditis was reached based on the exclusion of other relevant conditions, yet these patients were modelled to receive no risk reduction of MACE. ESC queried this rationale, as it considered a diagnosis by exclusion to still be a diagnosis, and that patients would still receive monitoring for a diagnosis reached through exclusion. ESC noted patients without obstructive CAD would receive prophylactic anti-platelet therapy for at least one year in line with the National Heart Foundation (NHF)–CSANZ guidelines.

ESC noted the ICER for population 2 was $15,787 per QALY. ESC considered the avoidable costs of placing potential myocarditis patients on unnecessary prophylactic ACS medications also contributed to the cost-effectiveness of cardiac MRI in this population. ESC noted that the key drivers of this ICER were time horizon, risk reduction of MACE, probability of MACE, cost of cardiac MRI, and cost of prophylactic ACS medications.

ESC raised concerns whether the claimed 50% reduction in the use of CTCA±TTE (from expert opinion) would be realised in practice as in its experience patients would likely undergo CTCA±TTE to rule out CAD before cardiac MRI. ESC noted additional scenario analyses were modelled utilising cardiac MRI as a second line investigation after CTCA ±TTE in patients without obstructive CAD. ESC noted that the ICER for cardiac MRI as a second-line test was $21,426 per QALY. A further scenario analysis adding weighting of CTCA and ICA (50% weighted distribution of CTCA and ICA) further increased the ICER to $39,210 per QALY.

ESC noted that compared to population 1, a higher proportion of patients in population 2 had LGE changes in their MRI (39% vs 48% respectively). Further to this, ESC considered population 2 to be a broad low-risk patient group in which realistically all patients will go on to receive medications and monitoring after any investigative test(s). Thus, ESC considered it was unrealistic to assume a change in management relative to the comparator, given the lack of evidence demonstrating a change in management.

ESC noted the utilisation and financial impact calculations used an epidemiological approach, which it considered was appropriate. ESC noted for population 1 the total cost to the MBS was estimated to be $3.685 million in year 1 increasing to $3.951 million in year 6; for population 2 the total cost to the MBS was estimated to be $1.401 million in year 1 increasing to $1.502 million in year 6.

However, ESC considered the estimated utilisation to be highly uncertain due to the multiple assumptions that were required to estimate the financial impact. In particular, ESC considered the reduced use of CTCA±TTE had been overestimated, meaning the financial cost for population 2 had highly likely been underestimated. ESC also considered the risk of leakage for population 1 was high, as cardiac MRI is performed to allow a differential diagnosis when patients with heart failure do not improve.

ESC noted the financial impact estimates were sensitive to the incidence of myocarditis, proportion of patients in population 1 vs 2, and the uptake rate of cardiac MRI.

ESC acknowledged that cardiac MRI can also provide an accurate diagnosis of several other cardiac conditions. ESC considered that the DCAR underestimated some of the benefits of cardiac MRI by using a binary, rather than composite, approach. As a result, ESC considered that the DCAR did not assess some benefits of cardiac MRI, such as for allowing a diagnosis of pericarditis – although ESC acknowledged that this may be difficult to model.

ESC also raised whether data were available to demonstrate that reducing uncertainty in a cardiac-related diagnosis improves health outcomes, but conceded these data were likely not available.

17. Applicant comments on MSAC's Public Summary Document

The cost impacts were evaluated based on the proposed item number rebate in the application that was consistent with the current new items for vaccine myocarditis and ARVC (both being around $850), however the descriptor has subsequently been left blank with regards to the proposed new item number rebate. It is unclear how an economic assessment was made using a cost that was not quantified.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)