Australian Government

Department of Health

Application 1464:

Breast Magnetic Resonance Imaging (MRI)

PICO Confirmation

(to guide a new application to MSAC)

(Version 1.0)

This PICO Confirmation Template is to be completed to guide a new request for public funding for new or amended medical service(s) (including, but not limited to the Medicare Benefits Schedule (MBS)). It is relevant to proposals for both therapeutic and investigative medical services.

Please complete all questions that are applicable to the proposed service, providing relevant information only.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment (HTA Team) on the contact number and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Document History

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0.1	10 March 2016	MSAC Reforms	Final for Publication
0.2	19 May 2016	MSAC WEB	Accessibility compliance

Document Approval

Version Number	Date Changed	Author	Reason for Change
1.0	19 May 2016	MSAC Web	Document released for Online publication

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

Population A: Diagnosis

Component	Description
Patients	Women with symptoms of breast cancer in which prior imaging has been inconclusive for the presence of breast cancer and biopsy has not been possible (e.g. possible distortion on only one mammographic view without a sonographic correlate).
Prior tests (for investigative medical services only)	• Clinical examination • Mammography • Ultrasound • Biopsy not possible (due to inability to locate lesion for biopsy)
Intervention	breast MRI
Comparator	No breast MRI
Reference standard	Histopathology or clinical follow up
Outcomes	Safety • Any adverse events arising from the addition of breast MRI • gadolinium reaction • claustrophobia • other Effectiveness Health and other patient-relevant outcomes: • Overall survival • Breast cancer specific mortality

Component	Description

	• Breast cancer recurrence
	• Quality of life
	• Patient preference
	• Satisfaction
	• Anxiety
	
	Diagnostic accuracy:
	
	• target condition is presence of primary breast cancer
	   ○ negative & positive predictive value,
	   ○ sensitivity & specificity
	   ○ ratio additional true/false positives
	
	Change in management:
	
	• Further testing avoided: open biopsy rate
	• Further testing instigated: biopsy, MRI-guided biopsy rate
	
	Other intermediate outcomes
	
	• Time to diagnosis
	• Time to initial treatment for breast cancer
	
	Impact on health outcomes of management changes based on MRI results:
	
	• Impact on survival of earlier diagnosis and treatment if MRI true positive (versus diagnostic delay if no MRI and 6 month follow-up)
	• Impact on quality of life of early rule-out diagnosis if MRI true negative (versus diagnostic delay if no MRI and 6 month follow-up; or adverse effects of open biopsy)
	• Impact on survival and quality of life if treatment delay due to MRI false negative (versus open biopsy)
	• Adverse events of biopsy if MRI false-positive (versus 6 month follow-up with no biopsy)
	
	Healthcare resources
	
	Total Australian Government healthcare costs including:
	
	• Cost of MRI
	• Cost of additional specialist consultations
	• Cost of biopsy
	• Cost of surgery
	
	Cost of follow up treatment

Research question: what is the safety, effectiveness and cost effectiveness of the addition of breast MRI to standard imaging in women with symptoms of breast cancer in which prior imaging has been inconclusive for the presence of breast cancer and biopsy has not been possible?

Population B: Pre-surgical planning

Component	Description
Patients	Women newly diagnosed with invasive breast cancer to offer local staging where MRI may alter treatment planning. Specifically women with a significant discrepancy between clinical examination findings and conventional imaging (mammography and ultrasound), which is likely to occur more frequently in women: • Aged less than 50 years • With very dense breasts • With invasive lobular breast cancer.
Prior tests (for investigative medical services only)	• Clinical examination • Mammography • Ultrasound • Biopsy
Intervention	Breast MRI
Comparator	no Breast MRI
Reference standard	Histopathology or clinical follow up
Outcomes	Safety • Any adverse events arising from the addition of breast MRI • gadolinium reaction • claustrophobia • other Effectiveness Health and other patient-relevant outcomes: • Overall survival • Breast cancer specific mortality • Breast cancer recurrence • Quality of life • Patient preference • Satisfaction • Anxiety

Component	Description

	Diagnostic accuracy:
	
	• Target condition is the extent of primary breast cancer, including detection of tumour > more than one quadrant, tumour stage (0-2cm, >2-5cm, 5+cm) multifocal/multicentric disease, contralateral disease, lymph node involvement
	  o negative & positive predictive value,
	  o sensitivity & specificity
	  o ratio additional true/false positives
	
	Change in management:
	
	• Biopsy rate
	• Change of stage
	• Change in surgical management: breast conserving surgery (BCS), mastectomy, sentinel node biopsy, axillary dissection
	• Change in neo/adjuvant therapy plan: neoadjuvant therapy, adjuvant therapy, radiotherapy
	• Ability to do or change in oncoplasty procedure
	
	Other intermediate outcomes
	
	• Time from diagnosis to definitive treatment eg. initial surgery
	• Time to breast reconstruction
	• Negative surgical margin rate
	• Reintervention rate eg. re-excision
	• cosmesis
	
	Impact on health outcomes of management changes based on MRI results:
	
	• Impact on recurrence rates, survival and quality of life of mastectomy vs BCS for cancers restaged by MRI (versus no MRI)
	• Impact on recurrence rates, survival and quality of life of other specified treatment decisions eg. radiotherapy, neo/adjuvant chemotherapy, oncoplasty for cancers restaged by MRI (versus no MRI)
	
	Healthcare resources
	
	Total Australian Government healthcare costs including
	
	• Cost of MRI
	• Cost of biopsy
	• Cost of surgery/s

Component	Description
	• Cost of follow up treatment

Research question: What is the safety, effectiveness and cost-effectiveness of the addition of breast MRI to standard imaging in women newly diagnosed with invasive breast cancer to offer local staging where MRI may alter treatment planning?

Population

Breast cancer is the most common cancer in women, comprising approximately 28% of all cancers diagnosed in women. In 2012, 15,337 women were diagnosed with invasive breast cancer while 2,349 women were diagnosed with ductal carcinoma in situ, the pre-cursor to invasive breast cancer. The number of women diagnosed with invasive breast cancer is projected to increase to 17,586 in 2017 (AIHW 2017). Five year relative survival from breast cancer in 2009-2013 was 90.2%, nevertheless there were 2,814 deaths from breast cancer in women in 2014 and this is projected to increase to 3,087 in 2017, the second leading cause of cancer-related death in women behind lung cancer (AIHW 2017).

Two patient populations have been proposed:

Population A: Diagnosis
> The use of MRI to characterise a lesion when other imaging examinations, such as ultrasound and mammography, and physical examination are inconclusive for the presence of breast cancer, and biopsy has not been possible (e.g. possible distortion on only one mammographic view without a sonographic correlate).

Expected utilisation

The applicant has not provided data to enable estimation of population A (diagnosis). For this population, the denominator would be women with a breast abnormality and not women diagnosed with breast cancer which is more difficult to estimate. Approximately 54% of women aged 50 to 74 years participate in the national BreastScreen program (Australian Institute of Health and Welfare 2016). Women with screen detected abnormalities are recalled for assessment. In 2014, 12% of women screening for the first time and 4% of women attending subsequent screens were recalled for further investigation (36,123 women in total)(Department of Health and Ageing 2009, Australian Institute of Health and Welfare 2016). Some of these women have clinical, mammogram or ultrasound findings that remain inconclusive after imaging and (attempted) biopsy and would be eligible for breast MRI if funded for Population A. Currently, these women are referred to open biopsy or advised to return for early review at 3-6 months. Thus BreastScreen rates of open biopsy and early review can be used for a lower level estimate of the population size. In 2005, 9.8% of women recalled had a FNA biopsy and 22.6% had a core biopsy. Of these biopsies, 11.5% of FNAs and 2.2% of core biopsies were inadequate (Department of Health and Ageing 2009). If the women with inadequate biopsies were eligible for breast MRI, this would give a lower level estimate of 1,603 women per year.

Rationale

The current approach to reach a diagnosis in Population A is to recommend the patient have an open (surgical) biopsy or return for review in 6 months for repeat examination and imaging. The use of breast MRI is proposed to avoid the need for open biopsy if the MRI is negative for cancer; and avoid delaying diagnosis for patients who would otherwise be recommended for early review.

<u>Population B: Surgical planning</u>

> The use of MRI in women newly diagnosed with cancer to offer local staging when conventional imaging with mammography and US is likely to under stage the disease. Specifically this includes women with a significant discrepancy between clinical examination findings and conventional imaging findings where the confirmation of more extensive disease on MRI would alter management. This is likely to occur more frequently in women diagnosed with breast cancer under 50years, those with very dense breasts, and in some subtypes of breast cancer such as invasive lobular breast cancer.

Although breast cancer is common, the proposed patient populations are a small sub-group of the incident cases, the majority of which are expected to be adequately assessed with conventional imaging.

Expected utilisation for Population B

The application has used data from two large audits at Royal Perth Hospital and the Mater Hospital, North Sydney to estimate the number of patients likely to utilise breast MRI for surgical planning.

At the Mater Hospital, 1,416 women were newly diagnosed with breast cancer between April 2010 and the end of 2015, and 177 (12.5%) were referred for a staging MRI. At Royal Perth Hospital, 1,499 breast cancers were diagnosed between 2011 and 2013 and 102 underwent MRI (6.8%). This estimate includes women where were diagnosed at the hospital (including via BreastScreen Assessment clinics) but who went for treatment elsewhere and may have had a private MRI, if only women who were treated at Royal Perth Hospital are included then the estimate is 962 diagnoses and 102 MRIs (10.6%).

If the upper estimate of 12.5% of total diagnoses is used, then the estimated utilisation for 2017, based on the AIHW estimate of 17,586 new cases, is 2,110. This estimate is lower than that of 3,300 made in MSAC assessment 1333, in which estimates were made using an epidemiological approach based on combining specific population subgroups (lobular cancer, dense breasts).

The use of pre-operative breast MRI is a quality indicator in the Netherlands where its use was found to vary wildly between hospitals (2014: range 4–84%, mean 31%) (van Bommel, Spronk et al. 2017).

<u>Rationale</u>

The current approach to surgical planning without MRI requires surgeons to take into account uncertainty about the extent of disease in treatment decisions. The type of clinical decisions that MRI can inform include:

- BCS versus mastectomy (or extent of excision)
- Unilateral versus bilateral surgery
- Sentinel node biopsy versus axillary dissection versus completion axillary clearance after SLN biopsy

- Neoadjuvant versus adjuvant chemotherapy
- Extent of radiotherapy field or if DXT needed
- Type or timing of oncoplastic procedure
- Need for second surgery

The clinical audit from the Mater Hospital provides information about the reasons for using pre-operative MRI (Table 1). Almost a third were due to a discrepancy between the clinical findings and conventional imaging as per the population proposed. Invasive lobular cancer and density were also cited frequently (13% and 23% respectively) and are included as part of the population description. Another third of cases did not appear to be well covered by the population description, most notably 'suspicion of multifocal disease'.

Table 1 Reasons for pre-operative MRI staging (Mater Hospital North Sydney, 2010-2015)

Reasons for pre-operative MRI staging (n=177)	n	%
Clinical mass larger than imaging	55	31
Imaging dense/unclear	41	23
Suspicion of multifocal disease	25	14
Invasive lobular cancer	23	13
Assessment of contralateral breast	13	7
Mass forming DCIS	11	6
Paget's disease with occult imaging	3	2
Mass-imaging occult	3	2
Mammoplasty planned at cancer surgery episode	3	2
Total	**177**	**100**

The surgical planning population is similar to that assessed in MSAC application 1333 in which the relevant proposed patient groups were defined as follows:

1) women newly diagnosed with the invasive lobular subtype of breast cancer, where conventional imaging frequently underestimates the extent of disease;
2) women newly diagnosed with invasive breast cancer who are
   a) <50 years of age, and/or
   b) with very dense breasts, and/or
   c) with a significant discrepancy (>1cm) between mammography and ultrasound, where conventional imaging frequently underestimates the extent of the disease
   d) have suspicious/malignant calcifications which may underestimate the extent of ductal carcinoma in situ (DCIS) disease.

It is also similar to the UK's NICE guidelines on early and locally advanced breast cancer diagnosis and treatment (National Collaborating Centre for Cancer 2009) which state:

- The routine use of MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or DCIS.

- Offer MRI of the breast to patients with invasive breast cancer:
  - if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment
  - if breast density precludes accurate mammographic assessment
  - to assess the tumour size if breast conserving surgery is being considered for invasive lobular cancer.

The population described in the application is defined by less specific criteria than it was for application 1333 and is also less specific than the NICE guidelines. This application is not intended to enable routine use of pre-operative MRI, but to enable access for a small number of women in whom it is indicated based on clinical judgement.

Prior test (investigative services only - if prior tests are to be included)

After presenting with either a palpable lump or an abnormality noted on a screening mammogram, patients undergo triple assessment:

- clinical examination
- imaging (mammogram and ultrasound)
- pathological assessment

Mammography (MBS 59300, 59301, 59303 and 59304) and breast ultrasound (MBS 55059, 55060, 55061, 55062, 55070, 55073 and 55076) are used to image breast cancer, they would continue to be the prime breast imaging modalities (conventional imaging) with MRI an additional test in selected women.

Rationale

Ultrasound has been considered an optional test in prior assessments of breast MRI. It is proposed that ultrasound be considered part of standard conventional imaging and a required prerequisite to breast MRI.

Intervention

Magnetic resonance imaging (MRI) uses a strong external magnetic field to produce images of biological tissues. This magnetic field acts on hydrogen protons (elementary particles) in body tissues and a radiofrequency pulse is used to produce signals that vary according to their local chemical, structural and magnetic environment. MRI is particularly well suited to distinguishing between blood vessels, other fluid filled structures and surrounding soft tissues, and as such is especially useful in imaging the brain, muscles and the heart as well as detecting abnormal tissues such as tumours.

Breast MRI is performed in a dedicated MRI room using an MRI machine with minimum magnet strength of 1.5 Tesla. A dedicated breast coil, compromising of 7 or more channels is also required and intravenous contrast is administered by powered or electronic injector. As breast tissue

generally has similar signal intensity to tumour tissue on routine MRI, the intravenous administration of a contrast agent containing gadolinium chelate is used to enhance breast lesions.

During the examination the patient lies prone on the MRI table with the breast dependant in the dedicated breast coil. A number of imaging sequences are obtained, prior to the administration of the contrast agent gadolinium. Following contrast injection further sequences are obtained including evaluation of the uptake and washout of contrast by breast tissue and any focal lesion over several minutes.

The MRI sequences obtained are interpreted by a radiologist to analyse the findings on the various sequences, including enhancement patterns. The aim is to distinguish between normal, benign and malignant findings. Malignant lesions usually display an enhancement pattern with rapid uptake and washout of contrast. In benign masses the contrast uptake is usually slower and more prolonged. Some lesions have atypical or indeterminate findings.

MRI can be used in both screening and diagnosis of breast cancer. This includes the identification of breast cancer in women with a high risk of breast cancer due to family history or genetic predisposition. Breast MRI is also used in preoperative staging, evaluating response to treatment, screening of women with breast augmentation or reconstruction and identification of occult breast cancer in women with metastatic disease.

Breast MRI can be undertaken in public or private hospitals or private radiology practices. An MBS funded MRI scan must be requested by a specialist or consultant physician (not a GP) and be performed on a Medicare-eligible MRI unit by a Medicare eligible provider, and be an MRI service listed in the MBS.

Currently, the MBS funds breast MRI for surveillance in asymptomatic high risk women under the age of 50 (MBS item number 63457, 63464), women with metastatic cancer restricted to the regional lymph nodes in whom the primary cancer has not been identified by conventional imaging (MBS item numbers 63487, 63488) and the evaluation of implant integrity (MBS item number 63501, 63502, 63504, 63505). MRI-guided biopsy is also funded for women in whom a biopsy guided by conventional imaging is not possible (MBS item numbers 63489, 63490).

For the indications proposed, only one test is likely to be required (unless a further MRI guided biopsy is required.)

Rationale

Not applicable, the intervention is clearly defined.

Comparator

No breast MRI (clinical decision based on prior tests alone)

Rationale

The comparator is clearly defined.

Outcomes

Population A: diagnosis

The proposed role of breast MRI is to more accurately diagnose breast cancer in patients when conventional imaging is inconclusive and a biopsy has not been possible. The proposed advantages of using MRI in these indications are:

- Breast MRI is a more sensitive test for the detection of breast cancer than mammogram and ultrasound
- May lead to improved health outcomes by avoiding either:
    - an open surgical biopsy and associated risk, or
    - repeat imaging in six months and associated patient anxiety
- May reduce time to definitive diagnosis and treatment, therefore reducing risk of recurrence and improving overall survival.

The potential disadvantages of using breast MRI in these indications are:

- Lower test specificity than mammogram and ultrasound
- May reduce health outcomes by
    - Increasing time to definitive diagnosis
    - Increasing rates of invasive procedures
- The additional cost of the test

Population B: surgical planning:

The proposed role of breast MRI is to more accurately stage the disease and it is expected that this will alter treatment for some women, most commonly from breast conserving surgery to mastectomy, which then translates into improved health outcomes. The proposed advantages of using MRI in these indications are:

- Breast MRI is a more sensitive test
- May lead to improved health outcomes by better selecting patients for breast conserving surgery thus,
    - Increasing rates of negative margins
    - Reducing rates of reintervention
    - Decreasing conversion from breast conservation to mastectomy at a later date
    - Reducing breast cancer recurrence
    - Increasing breast cancer survival.

    Similarly, the main advantages of using breast MRI to inform other treatment decisions about neoadjuvant chemotherapy versus adjuvant chemotherapy, more extensive axillary staging procedures, more extensive radiotherapy are to improve tumour control by reducing recurrence rates and improving survival.

- May also inform planning of oncoplastic procedures with improved health outcomes by allowing planning of one more extensive operation and planning to remove more extensive or multifocal/centric disease in one operation

The potential disadvantages of using breast MRI in this indication are:

- Lower test specificity
- May lead to reduced health outcomes by
  - Increasing rates of unnecessary mastectomies, including bilateral mastectomy
  - Increasing time between diagnosis and treatment
- The additional cost of the test

Patient relevant

For population A (diagnosis), additional patient relevant health outcomes include early reassurance and reduced anxiety following a negative test, and convenience due to avoiding further testing.

For population B (pre-surgical planning), additional patient relevant health outcomes are reassurance that surgery planning is based on the most sensitive imaging test information available.

Healthcare system

For both populations, the key outcomes for the healthcare system are the additional cost of the test and the change in cost due to additional biopsies and different surgical approaches.

Rationale

As noted, this application is for the use of breast MRI in non-routine populations. The proposal is to use breast MRI where conventional imaging and clinical examination have been undertaken and there remains uncertainty, it is expected that this is a very small sub-set of the overall population. Therefore, although these outcomes are appropriate, the majority of studies are conducted in routine populations and reporting these outcomes in routine populations may underestimate the benefit of MRI in 'problem solving' situations.

It will therefore be necessary for the primary assessment of evidence to be restricted to data from studies where the majority of patients have been selected to represent situations of uncertainty where additional information from MRI may guide clinical decisions; or report relevant outcomes for these subgroups.
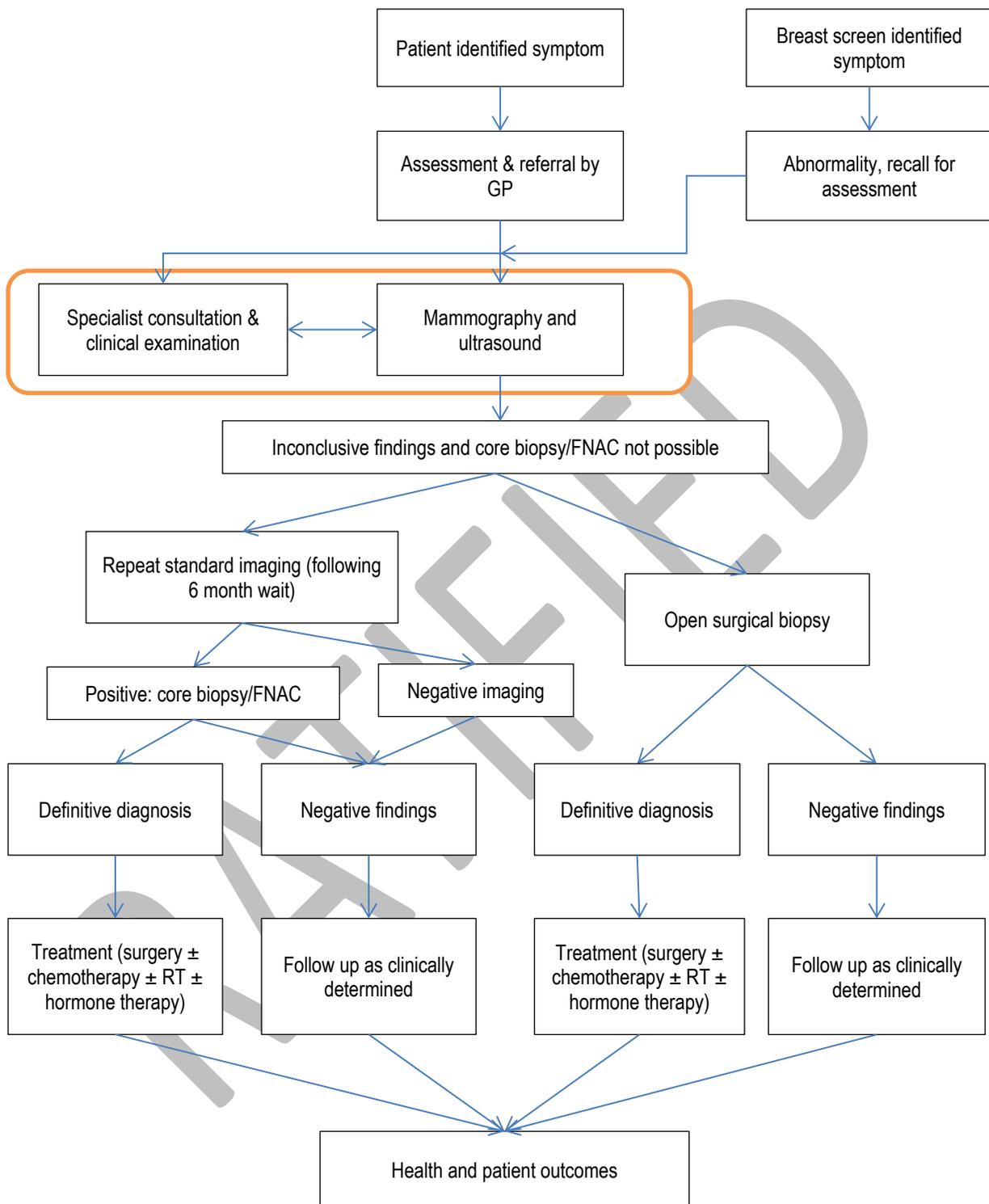
Figure 1 Current clinical management algorithm for population A: diagnosis

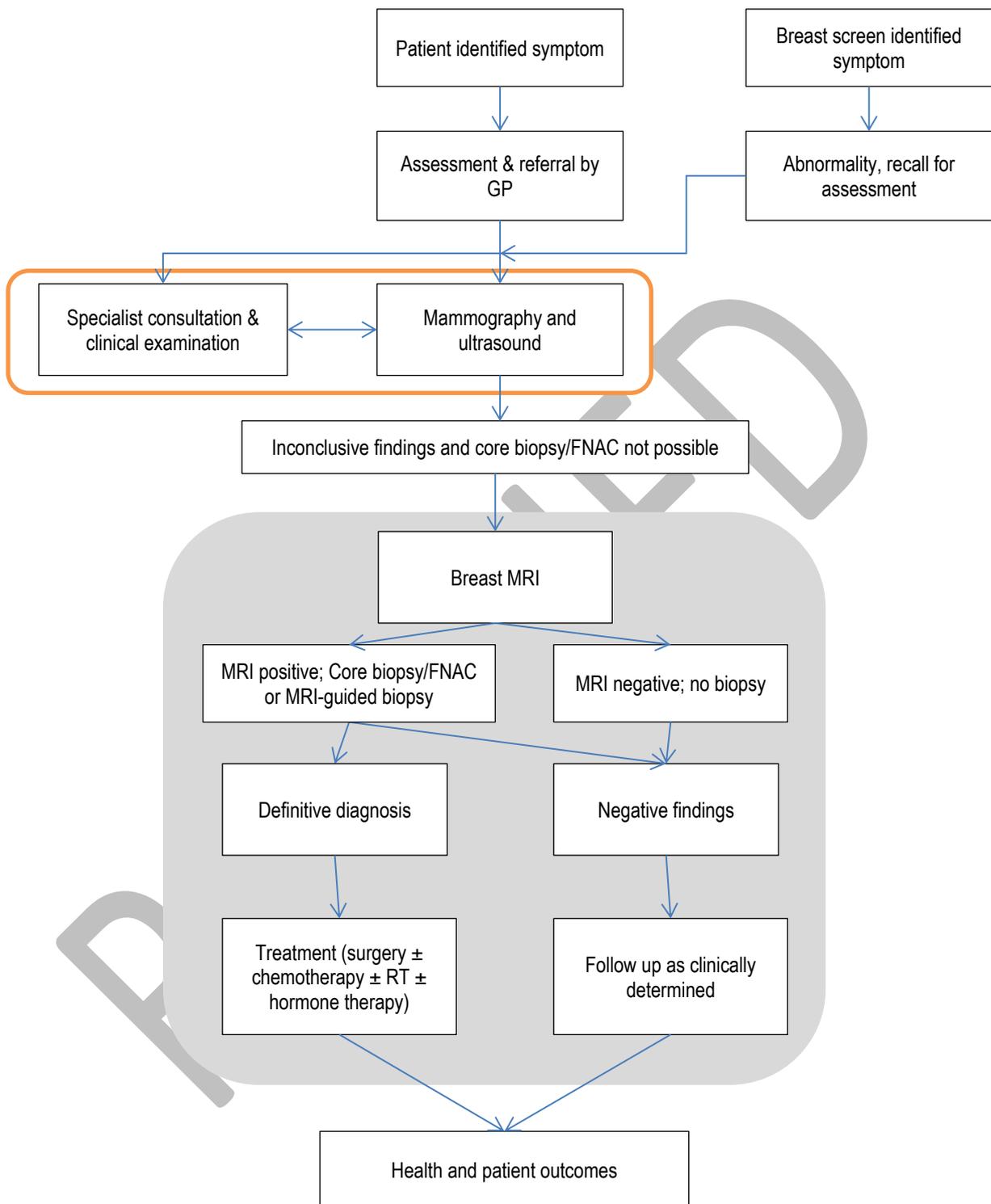*Proposed clinical management algorithm for population A: diagnosis*

Figure 2 Proposed clinical algorithm for population A: diagnosis
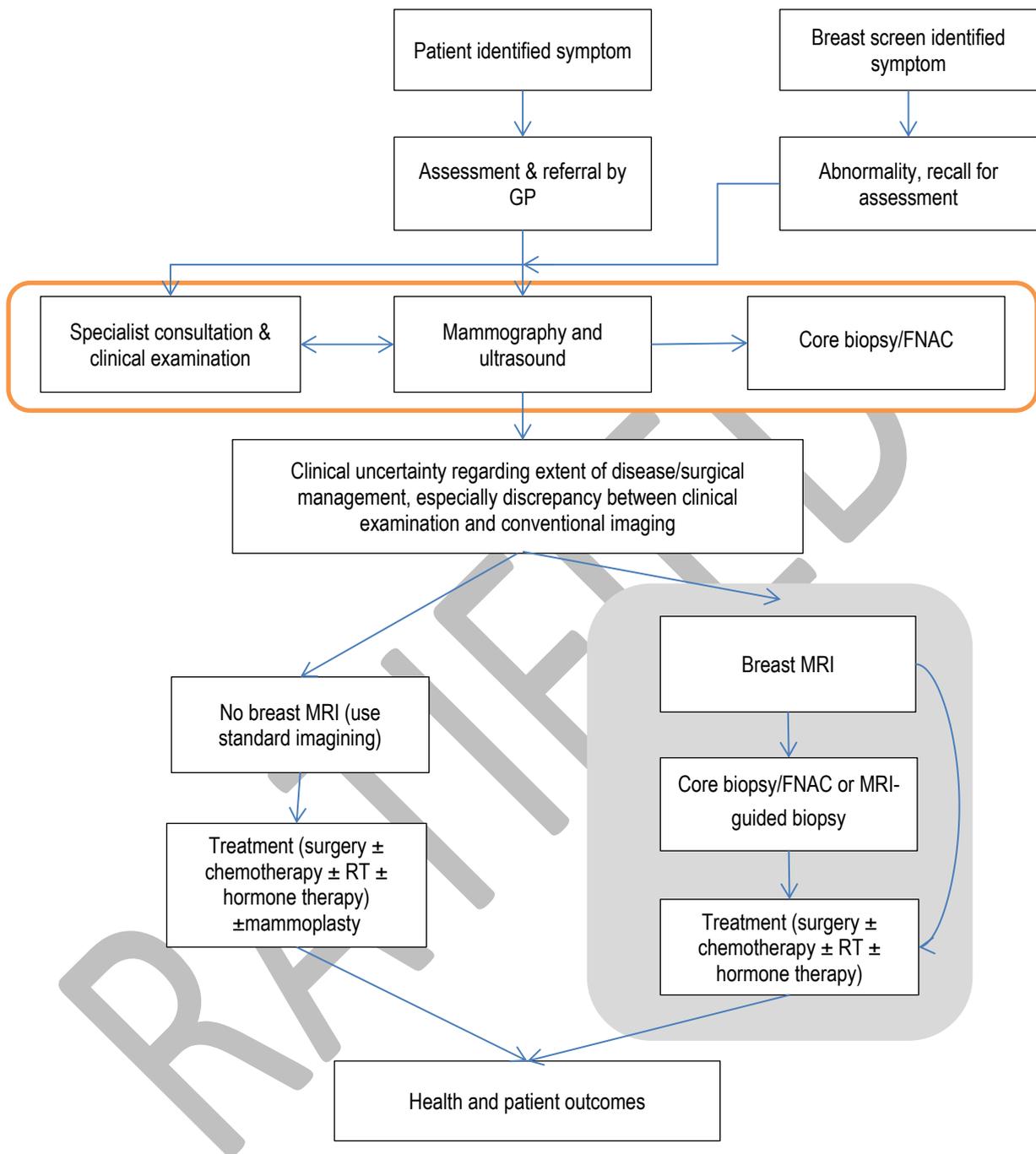
Figure 3 Proposed (shaded) and current (unshaded) clinical management algorithm for Population B: surgical planning

Proposed economic evaluation

It is proposed that breast MRI, for both populations, has non-inferior safety and superior clinical effectiveness. Therefore the appropriate type of economic evaluation is a cost-effectiveness analysis or a cost-utility analysis.

However, it should be noted that an exploratory cost-effectiveness analysis of breast MRI undertaken in application 1333 found no evidence of improved effectiveness or cost, and therefore a different approach would be required to support a claim for public funding.

Proposed item descriptor

Table 2   Proposed MBS item descriptor

Category 5 – Diagnostic imaging services

MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where:
a) A dedicated breast coil is used; and
b) The request for scan identified either:
    i.   That the patient has been diagnosed with a breast cancer and discrepancy exists between clinical assessment and conventional imaging assessment and breast MRI may alter treatment planning;
    ii. That the patient has a breast lesion which on other imaging examinations, such as ultrasound, mammography and physical examination are inconclusive for the presence of breast cancer, and biopsy has not been possible (e.g. Possible distortion on only one mammographic view without sonographic correlate).
 	
Fee: $690

Other considerations about evidence requirements for this assessment

The planned assessment will not be able to draw meaningful conclusions to inform decision-making if inadequate evidence is available to estimate the impact of breast MRI on health outcomes. MSAC Application 1333 identified a large body of evidence (including randomised controlled trials and individual patient data metanalysis) on the use of MRI in the general population of women with a diagnosis of invasive breast cancer undergoing surgical planning; but very little evidence assessing the population sub-groups listed for surgical planning (including Population B). The assessment concluded that there is a large and consistent body of evidence demonstrating that despite detecting more disease, breast MRI is not shown to improve surgical outcomes or to reduce recurrence rates. Teasing out the impact of MRI in an imperfectly defined sub-population in which MRI may improve outcomes was not possible in that assessment.

It would be inefficient to replicate the prior assessment undertaken for application 1333. Therefore this document explicitly defines the prior tests and common clinical decisions that MRI is proposed to inform in this subpopulation on page 9 to guide the selection of appropriate study populations and outcomes for the systematic review. If the initial search does not identify any studies reporting data on these relevant patients groups (defined by diagnosis and management uncertainty following prior tests) and outcomes (direct impact on listed health outcomes; or accuracy, change in management and other intermediate outcomes required to estimate health outcomes), then it may not be worthwhile proceeding with the assessment.

Therefore, PASC has considered alternative approaches for evaluation to inform decision-making have been considered. These approaches include:

(1) extending existing clinical audits of clinical practice to collect data on the downstream impact of pre-diagnosis MRI for Population A and pre-surgery staging for Population B, including the type of management changes, the proportion of patients with management change based on MRI results, the prevalence of cancer (Population A) and cancer staging findings (population B), and costs, allowing a micro-costing analysis to be undertaken to inform a modelled analysis of effectiveness and cost-effectiveness. A concurrent audit of practices that do not use MRI would also be valuable to provide data for relevant comparisons such as negative margin rates and re-excision rates for estimates of impact on health outcomes.

(2) a survey of breast surgeons to attempt to gain clinical consensus on specific clinical indications and their likely utilisation. This survey could also include questions to determine what ratio of proposed benefits versus potential harms would be considered an acceptable trade-off to support the use of breast MRI. For example, for Population A, when considering the proposed benefits of a true positive MRI result to provide an earlier diagnosis than 6 month follow-up, leading to earlier definitive treatment, and the potential harm of a false positive MRI result leading to unnecessary biopsy and patient anxiety: what is the highest number of false positive MRI results per true positive case detected that would be acceptable to support the use of MRI? This information can be used to determine whether the evidence of MRI accuracy meets clinician-defined minimum performance criteria for its use in Population A.

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