MSAC application no 1190

Magnetic Resonance Imaging (MRI) for small bowel Crohn's disease and fistulising perianal Crohn's disease

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Assessment 1190 - Magnetic Resonance Imaging (MRI) for small bowel Crohn's disease and fistulising perianal Crohn's disease

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This report is a contracted technical report for use by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared for MSAC by *L Gordon, T Comans and P Scuffham* from *Griffith University Assessment Group* with the assistance of Health Expert Standing Panel members (Assoc Prof Damien Stella, *Prof Richard Mendelson*). The report was commissioned by the Department of Health on behalf of MSAC.

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The procedure

Magnetic Resonance Imaging (MRI) for the evaluation of small bowel Crohn's disease and fistulising perianal Crohn's disease. MRI allows accurate visualisation of the entire gastrointestinal tract through the acquisition of multi-planar images with high-contrast resolution of the tissue. Bowel distension is needed to obtain optimal visualisation and is achieved through the use of an enteric contrast material. MRI is believed to be beneficial over other modalities that emit ionising radiation which may be contraindicated in children and pregnant women or when patients are at risk of multiple diagnostic procedures.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from Griffith University was engaged to conduct a systematic review of the literature and an economic evaluation of MRI in Crohn's disease for the indications proposed.

Research questions: Six focused research questions were outlined in the Decision Analytic Protocol (DAP) to help inform the decision as to whether public funding should be supported:

What is the safety, effectiveness and cost-effectiveness of MRI small bowel compared with:

- Computer tomography (CT) or small bowel follow-through (SBFT) for the evaluation of disease extent in patients initially diagnosed with Crohn's disease with suspected small bowel involvement?
- CT and SBFT for the evaluation of patients with exacerbation/suspected complications of known Crohn's disease?
- Ultrasound (US) in pregnant women with suspected small bowel Crohn's disease?
- CT, SBFT or endoscopic assessment in the assessment of change to therapy in patients with small bowel Crohn's disease?

What is the safety, effectiveness and cost-effectiveness of MRI pelvis compared with:

- surgical assessment or endoanal ultrasound in patients with pelvic sepsis and fistulas associated with established or suspected Crohn's disease?
- surgical assessment or endoanal ultrasound in assessment of change to therapy in patients with pelvis sepsis and fistulas from Crohn's disease?

Assessment of MRI

1. Purpose of application

An application requesting MBS listing of MRI for patients with Crohn's disease was received from the Gastroenterology Society of Australia by the Department of Health and Ageing in July 2011. The application requests three new MBS Items including MRI for small bowel, pelvis and associated enteroclysis.

The application specifically looks at two populations: 1) MRI small bowel in patients with small bowel Crohn's disease, 2) MRI pelvis for patients with fistulising perianal Crohn's disease. The application is somewhat complex in that there are six specific indications involving a target group with mainly established Crohn's disease but also suspected Crohn's disease in pregnancy or patients with suspected perianal fistulas. In addition there are several comparators involved depending on the separate indications for MRI.

Small bowel and pelvis MRI is used in conjunction with enteric contrast material to achieve bowel distention (the exception to this is in pregnant women where the use of the contrast agent may not be used). As such small bowel MRI may involve preparatory drinking or enteral tube intubation about one hour before the test as well as insertion of an intravenous cannula for intravenous contrast. Similarly an MRI of the pelvis generally requires insertion of intravenous cannula and intravenous contrast. The actual MRI takes around 30 to 40 minutes depending on whether it is for the small bowel or pelvis.

2. Background

MRI for Crohn's disease is not currently funded under the MBS. An application requesting MBS listing of capsule endoscopy for the diagnosis of suspected small bowel Crohn's disease was not supported by MSAC (Application #1146, 27/07/2011). The application was re-submitted in July 2013 and is awaiting an outcome.

3. Prerequisites to implementation of any funding advice

To perform a MRI in patients with Crohn's disease, a specialist radiologist with expertise in interpreting MRI scanning and familiarity with Crohn's disease would be needed. The scan, in order to attract a rebate, must also be requested by a specialist medical practitioner or consultant physician and be performed on a Medicare-eligible MRI unit by a Medicare-eligible provider, and be an MRI service listed in the MBS.

MRI is currently available in public and private facilities in major centres in each state and territory. There are 339 Medicare-eligible MRI units across Australia. This comprises 170 units with full Medicare-eligibility and 169 units with partial Medicare-eligibility

4. Proposal for public funding

Tables 1 and 2 present the proposed MBS item descriptors for the six indications of this application.

Table 1: Proposed MBS item descriptor for MRI for small bowel Crohn's disease with and without contrast agent

Category 5 – Diagnostic Imaging Services

MRI to evaluate small bowel Crohn's disease. Medicare benefits are only payable for this item if the service is provided to patients for : (a) Evaluation of disease extent at time of initial diagnosis of Crohn's disease (b) Evaluation of exacerbation/suspected complications of known Crohn's disease (c) Evaluation of known or suspected Crohn's disease in pregnancy (d) Assessment of change to therapy in patients with small bowel Crohn's disease NOTE 1: Assessment of change to therapy can only be claimed once in a 12 month period. Fee: $627.50 Benefit: 75% = $470.63 85% = $533.38
MRI enteroclysis for Crohn's disease. Medicare benefits are only payable for this item if the service is related to item XXXX : Fee: $265.25 Benefit: 75% = $198.94 85% = $225.46

Table 2: Proposed MBS item descriptor for MRI for fistulising perianal Crohn's disease

Category 5 – Diagnostic Imaging Services
MRI for fistulising perianal Crohn's disease. Medicare benefits are only payable for this item if the service is provided to patients for: (a) Evaluation of pelvic sepsis and fistulas associated with established or suspected Crohn's disease (b) Assessment of change to therapy of pelvis sepsis and fistulas from Crohn's disease NOTE 1: Assessment of change to therapy can only be claimed once in a 12 month period. Fee: $403.20 75% = $302.40 85% = $342.72

The Royal Australian and New Zealand College of Radiologists suggest separate descriptors and fees would be needed to distinguish between MR enterography and MR enteroclysis.

The item descriptors may need amending following MSAC discussions of this report.

The proposed fee for MRI small bowel is based on being similar in procedural complexity to MBS item 63473 for staging cervical cancer. For MRI pelvis, the proposed fee is based on being similar in complexity to MBS #63482 (MRI for pancreas and biliary tree). For MRI enteroclysis in small bowel, the fee is based on the cost of a nasojejunal tube $130 + procedure $135.25. The fees proposed seem appropriate.

5. Consumer Impact Statement

Consumers are likely to view a decision of public access to the proposed indications of MRI favourably. Patients currently have out-of-pocket expenses for MRI that may or may not be reimbursed through private insurers. Although a MRI procedure takes longer than the comparators, the procedure is non-invasive and may be substantially less embarrassing for patients with fistulising perianal disease requiring endoanal ultrasound (Siddiqui et al., 2012). Consumer feedback confirms that only some patients experience claustrophobia with MRI. Further, they suggest that funding faecal calprotectin, as a non-invasive marker of gut inflammation, needs to be considered to complement MRI for small bowel Crohn's disease. Increased access for rural and remote patients has recently occurred due to the MRI Expansion Initiative which increased the number of machines in rural areas.

6. Proposed intervention's place in clinical management

It is proposed that MRI will be indicated in six specific situations when evaluating patients with Crohn's disease and there are several proposed changes to current practice. These separate places in the clinical management algorithm are summarised in Table 3. Separate illustrations of the clinical algorithms are provided in Appendix A. In this assessment, the clinical evidence addressed the requirements of the agreed Protocol.

Table 3: Proposed indications of MRI and clinical place in therapy

Proposed Indication	MRI is intended to:
Evaluation of extent of disease at time of diagnosis for suspected or known Crohn's disease	Replace CT or SBFT
Evaluation of suspected complications in known Crohn's disease	Replace CT or SBFT
Evaluation of suspected Crohn's disease in pregnancy	Replace Ultrasound
Assessment of change to therapy in known Crohn's disease	Complement CT or SBFT or endoscopy
Evaluation of pelvic sepsis and fistulas suspected or known fistulising perianal Crohn's disease	Replace surgical examination or endoanal ultrasound
Assessment of change to therapy in patients with pelvic sepsis and fistulas in known fistulising perianal Crohn's disease	Complement surgical examination or endoanal ultrasound

CT = computer tomography, MRI = magnetic resonance imaging, SBFT = small bowel follow through.

7. Other options for MSAC consideration

The wording of the proposed MBS item descriptor does not fully reflect the intended use of patients with small bowel Crohn's disease. With the exceptions of women who are pregnant or those with suspected perianal disease, the evaluation of Crohn's disease with MRI is after initial assessment and diagnosis using other tests (i.e., ileocolonoscopy or endoscopy and histopathology tests). The MRI is designed for second-line testing in patients with established Crohn's disease and ongoing management. The proposed wording of the descriptor may require the addition of these prior tests or what the applicant defines as known Crohn's disease. This issue is important because the diagnosis of Crohn's disease can be achieved through many tests, usually ileocolonoscopy, but there is no 'gold standard'. However, a definitive diagnosis is crucial in Crohn's disease in Australia because it allows for certain PBS medications and biological therapies to be administered.

Furthermore, the proposed MRI service is required to be undertaken by a specialist radiologist with expertise in interpreting MRI scanning and familiarity with Crohn's disease. The scan must also be requested by a specialist medical practitioner or consultant physician.

MSAC may also wish to consider if there are limits to the number of MRIs that a patient can receive in a given time period for all six indications. Currently, once per 12 month period is stated in the descriptor for the two 'change in therapy' indications.

8. Comparator to the proposed intervention

The nominated comparators are; computer tomography (CT), small bowel follow through (SBFT) and ultrasound for the small bowel indications and endoanal ultrasound and surgical examination for the fistulising perianal Crohn's disease indications. The MBS item numbers are 56507 for CT with or without enterography, 58915 for SBFT, 55700 ultrasound and 55014 for abdominal/endoanal ultrasound. Other MBS items for CT and ultrasound may also be relevant. HESP advises that the vast majority of patients

with Crohn's disease currently receive CT in Australia. These comparators are appropriate.

9. Comparative safety

No studies were identified that report the safety outcomes of MRI compared with the nominated comparators. However, there are few perceived clinical issues around patient safety when performing MRI. On its own, MRI is non-invasive, does not emit ionizing-radiation and presents no chemical or bodily harm to the patient.

The main safety issues of MRI relate to:

- the procedure being in a confined space and potentially uncomfortable for patients with claustrophobic tendencies or anxiety disorders,
- the exclusion of patients with allergies to the contrast enteric material necessary to distend the bowel in preparation for the MRI and
- the exclusion of individuals with internal metal or magnetic devices that may malfunction.

Clinical management using MRI is widely viewed as being safer than CT, SBFT and surgical examination. MRI and ultrasound do not emit ionizing radiation and do not have the attendant risks of adverse events in surgery. Evidence suggests that CT results in small annual effective radiation doses but, in a small proportion of patients (7-15%) with Crohn's disease, the cumulative dose is considered excessive (Desmond et al., 2008, Kroeker et al., 2011). Higher susceptibility to cumulative radiation occurs in younger age and in abdominal structures. There is no direct evidence that radiation from imaging procedures in Crohn's disease results in increased cancer mortality. Some evidence suggests that cancer incidence is elevated in patients with Crohn's disease but this has not been linked to imaging procedures in the study populations (Jess et al., 2005, Pedersen et al., 2010).

10. Comparative effectiveness

The primary sources of evidence are six diagnostic accuracy studies, two 'change of management' studies and three systematic reviews. Two of the systematic reviews were assessed as being high quality (Siddiqui et al., 2012, Wu et al., 2013) and two diagnostic studies (Jensen et al., 2011, Schmidt et al., 2010) demonstrated good (NHMRC Level II) evidence for diagnostic studies.

Diagnostic performance of MRI small bowel is equivalent to the comparators for sensitivity and specificity. Across the studies, the sensitivity of MRI was high and consistent with the results from the systematic reviews (range 74% to 100%). Similarly, CT also produced high sensitivity across the studies (range 83% to 100%). The specificity of MRI was also high for the studies reporting this outcome (range 80% to 100%) but similar compared with CT (range 67% to 100%).The high-quality study by Jensen et al. (2011) found sensitivity and specificity results at the lower end of the overall range across all the studies. Statistical analysis showed that the sensitivity and specificity of MR enterography was not statistically significant from CT enterography (Jensen et al., 2011).

In a meta-analysis for MRI pelvis in fistulising perianal Crohn's disease for identifying fistulas, the pooled sensitivity of MRI was 87% (95%CI: 63%-96%) and specificity 69% (95%CI: 51%-82%). For endoanal ultrasound, pooled sensitivity was identical to MRI at 87% (95%CI: 70%-95%) but lower for specificity 43% (95%CI: 21%-69%) (Siddiqui et al., 2012).

No studies were found comparing the extent of Crohn's disease or complications of disease using SBFT as the comparator, all used CT for small bowel Crohn's disease. No studies reported outcomes for MRI in pregnant women most likely because the studies included CT and CT is contraindicated in pregnancy.

It is unclear if there is any direct or indirect impact on clinical or patient outcomes based from the evidence in this assessment.

11. Economic evaluation

A cost-utility analysis was performed for one of the six proposed indications; pelvis MRI for extent of Crohn's disease in fistulising perianal Crohn's disease. This was the only indication where a cost-utility analysis was justified based on the superior specificity of MRI to endoanal ultrasound (Siddiqui et al., 2012). The evaluation was a simple decision-analytic model with a 12 month time horizon. The analysis should be viewed as exploratory due to the absence of key estimates from an evidence base.

The main inputs to the economic model were the sensitivity and specificity estimates from the main supporting meta-analysis (Siddiqui et al., 2012), costs for MRI pelvis, costs for surgical procedures and endoanal ultrasound and utilities for patients with Crohn's disease. In the base case, the mean costs of a MRI strategy were lower over 12 months than a strategy of endoanal ultrasound (by $806), while the corresponding quality-adjusted life years (QALYs) were slightly higher (0.05). MRI pelvis therefore dominated endoanal ultrasound. Probabilistic sensitivity analyses showed a high likelihood of MRI being cost-effective for this indication and may be cost-saving in most cases, subject to the assumptions of the model.

12. Financial/budgetary impacts

- Likely volume of use of the proposed imaging test per year: 13597
- Frequency of use per patient per year over 5 years: 1 per year
- Patient numbers per year (prevalence/ incidence mix over time): 13597
- Total cost of the proposed imaging test to the MBS per year: $8,718,243
- Total cost of the service to the public: unknown
- Net financial cost/year to the MBS (without safety net impacts): $6,256,006

13. Other significant factors

Nil

14. Conclusions

The key clinical issues that remain a source of uncertainty for this assessment include:

1) The proposed patient population is predominantly for established Crohn's disease but the current proposed MBS item descriptors could target this population more definitively by defining the duration of disease or prior tests that must have been undertaken;

2) The diagnostic accuracy is based on satisfactory evidence for detecting extent and complications of disease. However the studies included in this assessment have

limitations relating to study heterogeneity, small sample sizes, and potential unblinding across the tests and reference standards. Furthermore, all studies are European-based and details of patient characteristics were minimally reported. Therefore, the applicability to an Australian population is unclear.

3) MRI test accuracy has an unknown impact on management decisions and in turn, patient outcomes. It is therefore unclear what benefits patients receive from MRI in addition to the comparators. The claim that the reduction in exposure to ionizing radiation is the central argument but there is unclear evidence of how harmful CT and SBFT are likely to be.

4) There were no comparative safety or effectiveness outcomes for pregnant patients suspected of Crohn's disease therefore conclusions cannot be drawn about the safety or effectiveness in this subgroup.

The key economic considerations include:

1) The lack of evidence on the epidemiology, actual utilisation of imaging modalities and clinical management patterns of Australian's with Crohn's disease. This hinders accurate estimates for the financial estimates and economic evaluation.

2) The main driver of the costs to the MBS and Australian health system for the proposed use of MRI here is the frequency of tests per person required for a disease that is incurable and chronic. The likelihood of MRI uptake is high and potentially rapid considering the high proportions of patients with Crohn's disease experiencing complications, complex disease and abscesses/fistulas.

3) The cost-utility model within this assessment is largely hypothetical and several assumptions were necessary during construction due to the absence of data. In this light, the analysis should be seen as exploratory until more robust estimates are available.

The likely repercussions of a rejection are likely to fall heavier on patients with suspected or known fistulising perianal Crohn's disease. This subgroup will be disadvantaged due to the uncomfortable and invasive alternatives in current use. However, relatively fewer consequences will be felt for those with small bowel Crohn's disease due to the alternative imaging options readily available and their equivalent diagnostic performance.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of magnetic resonance imaging (MRI), which is a diagnostic test for the management of Crohn's disease. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for MRI small bowel and pelvis in the evaluation of small bowel Crohn's disease and fistulising perianal Crohn's disease.

Background

Crohn's disease

Crohn's disease is most common in adolescents and young adults, but can occur at any age. Diagnosis is based on a composite of endoscopy, radiography and pathological findings. Crohn's disease is a lifelong condition which often requires repeat diagnostic investigations to evaluate and assess disease; patients may undergo imaging as frequently as several times a year or not at all depending on their progress and disease severity. As many as 50-60% of patients require surgery at some point, to manage their disease. Many require repeat surgery for recurrent disease despite treatment with pharmacotherapy. Management depends on the disease location, disease severity, and disease-associated complications (Zimmermann and Al-Hawary, 2011).

Magnetic resonance imaging (MRI)

MRI is not a new technology and it has been used in medical imaging since the 1980s. It involves the production of a magnetic field that causes hydrogen atoms in the body to align in a certain direction. When the field is switched off, the atoms return to their normal alignment sending off a signal that can be interpreted by a computer to produce images. There is no ionising radiation from an MRI scan as it uses magnetic and radio waves. Therefore there is no increased risk of cancer and it is theoretically safe in pregnancy. MRI is not suitable for people with metal implants as the magnetic field can dislodge metal parts, depending on their size and location. Also, MRI scans can cause pacemakers or defibrillators to malfunction.

MRI allows accurate visualisation of the entire gastrointestinal tract through the acquisition of multi-planar images with high-contrast resolution of the tissue. Bowel distension is needed to obtain optimal visualisation and is achieved through the use of an enteric contrast material. This may be administered orally (MR enterography) or through an nasojejunal tube (MR enteroclysis).

Small bowel MRI is used in conjunction with enteric contrast material to achieve bowel distension (the exception to this is in pregnant women where the use of the contrast agent may not be used). As such small bowel MRI may involve preparatory drinking or enteral tube intubation about one hour before the test as well as insertion of an intravenous cannula for intravenous contrast. Similarly an MRI of the pelvis generally requires insertion of intravenous cannula and intravenous contrast. The actual MRI takes around 30 to 40 minutes depending on whether it is for the small bowel or for pelvis. The individual is required to stay very still in a dark space for this time. Ear plugs are offered due to the loud knocking noise of the machine. This noise is not loud enough to cause pain or hearing damage to the individual.

Improvements in MRI technology such as fast scanning techniques and the use of bowel anti-peristaltic agents have permitted more accurate diagnosis of complications of Crohn's disease, including abscess, fistula and stenosis. MRI is widely believed to be useful when ionising radiation is contraindicated such as in children and pregnant women and where multiple diagnostic procedures are needed, as may occur in chronic, remitting and relapsing conditions such as Crohn's disease.

To perform a MRI in patients with Crohn's disease, a specialist radiologist with expertise in interpreting MRI scans and familiarity with Crohn's disease is needed. The scan, in order to attract a rebate, must also be requested by a specialist medical practitioner or consultant physician and be performed on a Medicare-eligible MRI unit by a Medicare-eligible provider, and be an MRI service listed in the MBS. All radiologists providing MRI services must demonstrate that they meet minimum MRI training requirements. The Department of Human Services (DHS) uses 'participation in the Royal Australian and New Zealand College of Radiologists (RANZCR) Quality and Accreditation Program' as one of the eligibility criteria under MRI Eligible Provider regulations. All eligible providers for MRI declare that they are participants in the Quality and Accreditation Program in their MRI Statutory Declarations to DHS, which means they are declaring that they are complying with MRI-specific requirements in the RANZCR Standards of Practice and the MRI Quality Program

Intended purpose

This report assesses MRI in patients with Crohn's disease. Collectively, the intended purpose of this application is for MRI to be used in patients who have previously been diagnosed with Crohn's and where the imaging is designed to investigate known disease to direct further treatment. Patients with suspected Crohn's disease are usually diagnosed with ileocolonoscopy and histopathology. The spectrum of uses in this application therefore goes beyond initial diagnosis of Crohn's disease. It focusses on patients with small bowel or pelvic Crohn's disease and the purposes of evaluating disease extent, complications, in pregnancy and informs any change of therapy required. Patients with suspected fistulising perianal Crohn's disease or are pregnant with suspected Crohn's disease are the exceptions.

Clinical need

Epidemiology of Crohn's disease

Quantifying the burden of Crohn's disease in Australia is difficult since there are few epidemiological studies on this topic and those that exist combine Crohn's disease with ulcerative colitis, known collectively as inflammatory bowel disease. However, in a recent prospective, population-based study of inflammatory bowel disease incidence, the Asia-Pacific Crohn's and Colitis Epidemiology Study, the crude annual overall incidence of Crohn's disease in Australia during 2011-2012 was 14.00 (95%CI: 10.09-18.92) per 100,000 persons (n=49) (Ng et al., 2013). This equates to approximately 3,220 new cases each year in Australia. In this study, there were slightly more females (51%) than males (49%) and all incident cases were Caucasians with a mean age of 40 years. The peak age of diagnosis was 20-24 years with a second smaller peak at 40-44 years. The ratio of Crohn's disease to ulcerative colitis in Australia was 2:1. Median time from the onset of symptoms to diagnosis was 5½ months (interquartile range 1.4 – 15 months) and 25% of patients were diagnosed as an inpatient. Complications of Crohn's disease by way of structuring, penetrating or perianal disease were found in 24% of patients and a family history was found in 17% of cases (Ng et al., 2013).

A report in March 2013 has estimated updated prevalence figures of inflammatory bowel disease for Australia (PricewaterhouseCoopers Australia, 2013). They report the disease affects approximately 75,000 Australians each year.

Impact on patient quality of life

Crohn's disease exerts a significant burden to individuals since it is an incurable chronic condition that manifests most commonly in adolescents and young adults. It substantially impairs quality of life due to the experience of symptoms such as abdominal pain and diarrhoea. Factors that concern patients include the uncertainty of the disease, adverse effects of medication, incontinence, having to use an ostomy bag, low energy levels and the possible need for surgery. These experiences can severely interrupt normal role activities and good quality of life. Aspects specifically related to fistulising perianal disease include: discharge, pain, restriction of sexual activity and time with the disease (Taxonera et al., 2009).

Mortality

Two meta-analyses have provided standardized mortality ratios for patients with Crohn's disease. A small but statistically significant increase in mortality (standardized mortality ratio 1.39 (95%CI: 1.3-1.49) has been reported (Duricova et al., 2010). The higher number of deaths relative to population norms was explained by increased deaths from gastrointestinal diseases (including Crohn's disease) as well as other diseases (COPD, lung disease and genitourinary disease). In a second study by Canavan *et al.* (2007) including 13 published studies from 1970, a meta-analysis found an elevated risk of mortality for individuals with Crohn's disease (standardized mortality ration 1.52 (95%CI: 1.32-1.74), $p<0.001$ (Canavan et al., 2007). However, many of the studies in the review do not reflect current clinical practice and improved therapies.

Hospital separations

In 2009-10, there were 16,756 hospital separations with the principal diagnosis of Crohn's disease (ICD code K50) (AIHW, 2011). Of these, 2,785 (16.6%) separations were for small bowel Crohn's disease (K50.1). Between 1998-99 and 2008-09, hospital separations for Crohn's disease (K50) increased 2.5-fold, increasing from 6,485 to 16,756 (AIHW, 2011). This is consistent with reported global increases in the prevalence of Crohn's disease; however it could also represent an increased rate of admissions per patient (Wilson et al., 2010, Zimmermann and Al-Hawary, 2011).

Existing tests

Diagnosis of Crohn's disease can be difficult as the symptoms for Crohn's disease mimic those of ulcerative colitis and other gastrointestinal conditions. Currently, there are no clinical, endoscopic or pathological markers for a definitive diagnosis of Crohn's disease. In the absence of an agreed 'gold standard' test, diagnosis of Crohn's disease is based on a combination of; clinical judgement on the basis of patient history, physical examination, radiographic and endoscopic evidence and histological and laboratory findings. Ileocolonoscopy is commonly used to diagnose Crohn's disease as first-line testing. In most cases, a definitive diagnosis of Crohn's can be made but sometimes results of ileocolonoscopy are indeterminate. Sometimes, this is due to ileocolonoscopy not allowing view the entire bowel. In this case, second-line imaging if often undertaken to confirm a diagnosis of Crohn's disease.

For assessing known Crohn's disease in the small bowel or pelvis, there are four existing imaging tests:

Abdominal computer tomography (CT)

Abdominal CT is a radiological technique used to examine the extent or complications of small bowel Crohn's disease. This test provides multiplanar images of the lumen, wall and mesentery of the small bowel. These images have a high degree of spatial resolution and are generated via the use of multidetector CT technology following intravenous contrast and the ingestion of a contrast agent by the patient either orally (CT enterography) or via a naso-jejunal tube (CT enteroclysis). Abdominal CT is funded under MBS item 56507 with a fee $480.05. A range of other MBS items for CT also exist.

Small bowel follow through (SBFT)

SBFT is a radiological technique for imaging the small bowel. Barium is either ingested by the patient or administered by enteroclysis and then x-ray images are taken of the abdomen. In some Australia settings, SBFT has been superseded by abdomen CT/CT enteroclysis however clinical practice varies across settings. Moreover, its use is limited by high radiation exposure. SBFT is funded under MBS item 58915 with a fee $78.95.

Endoanal Ultrasound

To perform endoanal ultrasound, a dedicated probe is required which can be attached to some standard ultrasound machines. Endoanal ultrasound is only used for perianal disease, as opposed to standard ultrasound which is used for gynaecological evaluation of the pelvis, renal tract or hepatobiliary-pancreatic tree. Expertise in Australia with endoanal ultrasound is limited as there is no formal training and the investigation is usually carried out by interested clinicians who may not have specific radiological training in ultrasound (Rieger et al., 2004).The main advantage with endoanal ultrasound is its ability to assess deep, complex fistulas accurately.

Surgical Examination

In practice, surgical examination (under anaesthesia) and exploration is undertaken to evaluate fistulising Crohn's disease. This consists of visual inspection, palpation and the passage of metal probes into fistula tracks under general anaesthesia. Surgical examination under anaesthesia is the gold standard in the evaluation and classification of acute deterioration of perianal sepsis in Crohn's disease. It is expensive however and carries the risk of damage to the anal sphincter during the procedure leading to incontinence.

Current guidelines

Updated Australian guidelines for inflammatory bowel disease have been available from the Gastroenterological Society of Australia in May 2013. These provide general practitioners and clinicians with specific diagnosis and treatment options and, where applicable, reference the current PBS and MBS reimbursed services and products. With respect to MRI and this application specifically, the guidelines state:

'Cross-sectional imaging (CT, ultrasonogragphy, MRI including CT enterography and MRI enterography). To determine disease extent and severity and to assess for perforating complications. Ultrasound and MRI are preferred as the patients are often young and are likely to require repeat imaging over time' page 11 (Gastroenterological Society of Australia, 2013).

Marketing status of technology

MRI is currently available in public and private facilities in major centres in each state and territory. There are 339 Medicare-eligible MRI units across Australia. This comprises 170 units with full Medicare-eligibility and 169 units with partial Medicare-eligibility.

MRI is subject to the capital sensitivity measure for all diagnostic imaging equipment. Most diagnostic imaging services (except for PET) have two different schedule items: schedule K items and schedule NK items. Schedule NK items have a fee approximately half the corresponding K item. Whether a service is a schedule K or a schedule NK service depends on the age of the equipment, whether the equipment has been upgraded or whether a location based exemption of the age requirements has been granted (see http://www.health.gov.au/capitalsensitivity).

In Australia, the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) uses Diagnostic Reference Levels on specified imaging protocols to help avoid excessive radiation doses to patients. This quality assurance tool is part of the ARPANSA Code of Practice (RPS 14) that must be complied with by accredited RANZCR radiologists. ARPANSA and other stakeholders are currently establishing a national survey program for the development of national Diagnostic Reference Levels with the first being applied to multidetector computer tomography (ARPANSA, 2013).

Current reimbursement arrangements

MRI is currently not listed for the diagnosis or ongoing assessment of known small bowel or pelvis Crohn's disease. For the proposed indications, MRI is currently funded by patients.

Approach to assessment

Objective

The objective of this assessment is to undertake a structured evaluation of the clinical need, safety, effectiveness and cost-effectiveness of MRI for patients with small bowel or fistulising perianal Crohn's disease.

Clinical decision pathway

For the six indications proposed in the application, there are six corresponding clinical decision flow charts for MRI for patients as provided in the final DAP. These flow charts are provided in Appendix A. Figure 1 provides a simplified clinical pathway to summarise the clinical place of the six MRI indications (shown in red numerals) proposed in this application. Table 4 provides the details of the corresponding relevant comparators for each indication.

Comparators

For the specific indications proposed in the application, there are six relevant comparators for MRI for patients with small bowel or perianal fistulising Crohn's disease:

Small bowel:

- CT
- Ultrasound (in pregnancy)
- SBFT
- Endoscopy

Fistulising perianal:

- Surgical examination
- Endoanal ultrasound

The reference standard

This application primarily targets patients initially diagnosed with Crohn's disease and the potential uses during the monitoring or management of the condition. MRI is intended for use in patients with established Crohn's disease, except for pregnant women who may have suspected Crohn's disease and are ineligible for prior tests and a small subgroup of patients with suspected perianal Crohn's disease.

Small bowel: There is no agreement as to the optimal gold standard and due to the advantages of MRI over the most common comparator CT, MRI may become the new gold standard. For small bowel Crohn's disease, the reference standard is a panel of tests (excluding the index or comparator tests).

Fistulising perianal: Surgical examination is considered the reference standard for fistulising Crohn's disease.

Figure 1: Simplified clinical decision tree

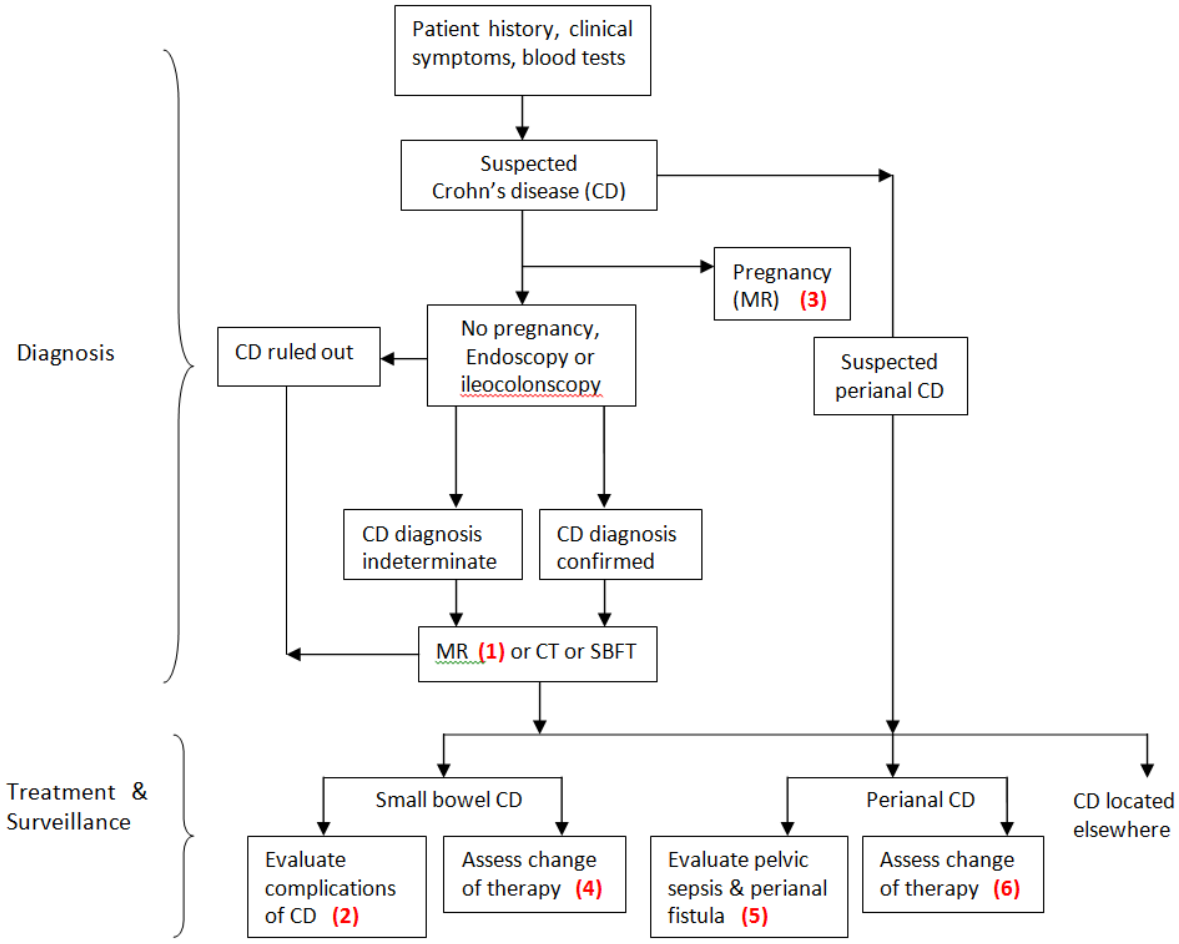


Table 4: Summary of indications for MRI application and replacement tests

Proposed Indication (numbers refer to Figure 1)	MRI to replace:
(1) Evaluation of extent of disease at time of diagnosis for suspected or known Crohn's disease	CT or SBFT
(2) Evaluation of suspected complications in known Crohn's disease	CT or SBFT
(3) Evaluation of suspected Crohn's disease in pregnancy	Ultrasound
(4) Assessment of change to therapy in known Crohn's disease	CT or SBFT or endoscopy
(5) Evaluation of pelvic sepsis and fistulas suspected or known fistulising perianal Crohn's disease	Surgical examination or endoanal ultrasound
(6) Assessment of change to therapy in patients with pelvic sepsis and fistulas in known fistulising perianal Crohn's disease	Surgical examination or endoanal ultrasound

CT = computer tomography, MRI = magnetic resonance imaging, SBFT = small bowel follow through.

Research questions

What is the safety, effectiveness and cost-effectiveness of MRI small bowel compared with:

- CT and SBFT for the evaluation of disease extent in patients initially diagnosed with Crohn's disease with suspected small bowel involvement?

- CT and SBFT for the evaluation of patients with exacerbation/suspected complications of known Crohn's disease?
- US in pregnant women with suspected small bowel Crohn's disease?
- CT, SBFT or endoscopic assessment in the assessment of change to therapy in patients with small bowel Crohn's disease?

What are the safety and effectiveness and cost-effectiveness of MRI pelvis compared with:

- surgical assessment and endoanal ultrasound in patients with pelvic sepsis and fistulas associated with established or suspected Crohn's disease?
- surgical assessment and endoanal ultrasound in assessment of change to therapy in patients with pelvis sepsis and fistulas from Crohn's disease?

Table 5 provides details of the PPICO criteria for assessment of diagnostic tests.

Table 5: PPICO criteria

Patients	Prior tests	Intervention	Comparator	Outcomes to be assessed
Patients with initial diagnosis of Crohn's disease with symptoms of small bowel involvement or patients with suspected Crohn's disease and are pregnant.	Clinical examination involving patient history, assessment of symptoms, blood tests. First line endoscopy, ileocolonoscopy and histopathology.	MRI small bowel including MR enterography or MR enteroclysis	CT enterography or CT enteroclysis SBFT Endoscopy Ultrasound (in pregnancy)	*Diagnostic performance* Sensitivity Specificity Additional TP and FP Diagnostic yield *Therapeutic impact* % change in management plans (for example from medical to surgery) *Patient outcomes* Impact of treatment on symptoms Activity of disease Development of complications Crohn's disease progression Treatment morbidity Quality of life
Patients with suspected or established fistulising perianal Crohn's disease	Clinical examination involving patient history, assessment of symptoms, blood tests.	MRI pelvis	Endoanal ultrasound Surgical examination	

CT = computer tomography, MRI = magnetic resonance imaging, SBFT = small bowel follow through, TP = true positives, FP = false positives.

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews for the period up to November 2013. Searches were conducted via MEDLINE, The Cochrane Library (including Cochrane Reviews, NHS-EED, DARE and HTA), clinical registers and HTA sites (Table 6). Reference lists of the selected studies were manually searched.

Table 6: Electronic databases searched

Database	Period covered
MEDLINE via OVID MEDLINE	Up to 11 November 2013
The Cochrane Library • NHS-EED • Cochrane Reviews • DARE • HTA	Up to 15 November 2013
Clinical Registers • Current Controlled Trials www.controlled-trials.com • ControlledTrials.gov www.clinicaltrials.gov • Australian New Zealand Clinical Trials Registry www.anzctr.org.au • WHO International Clinical Trials Registry Platform http://apps.who.int/trialsearch	
HTA websites • International Network of Agencies for Health Technology Assessment (INAHTA) http://www.inahta.org/ • NHS Centre for Reviews and Dissemination databases http://www.york.ac.uk/CRDweb	

The search terms used included 'Crohn' 'Crohn's' 'enteritis''enterocolitis' 'small bowel' 'pelvic sepsis' 'fistula''magnetic resonance' 'MRI' 'MRE' 'fistulising' and 'perianal'. Search terms were confined to the title, abstract or keywords fields. Full details of the search strategies are provided in Appendix B.

Title and abstracts were screened by two evaluators for potential relevance and omitted where appropriate. Of those remaining, full text articles were retrieved and examined in more depth.

Table 7 provides full details of the *a priori* inclusion and exclusion criteria used for the studies included for this assessment.

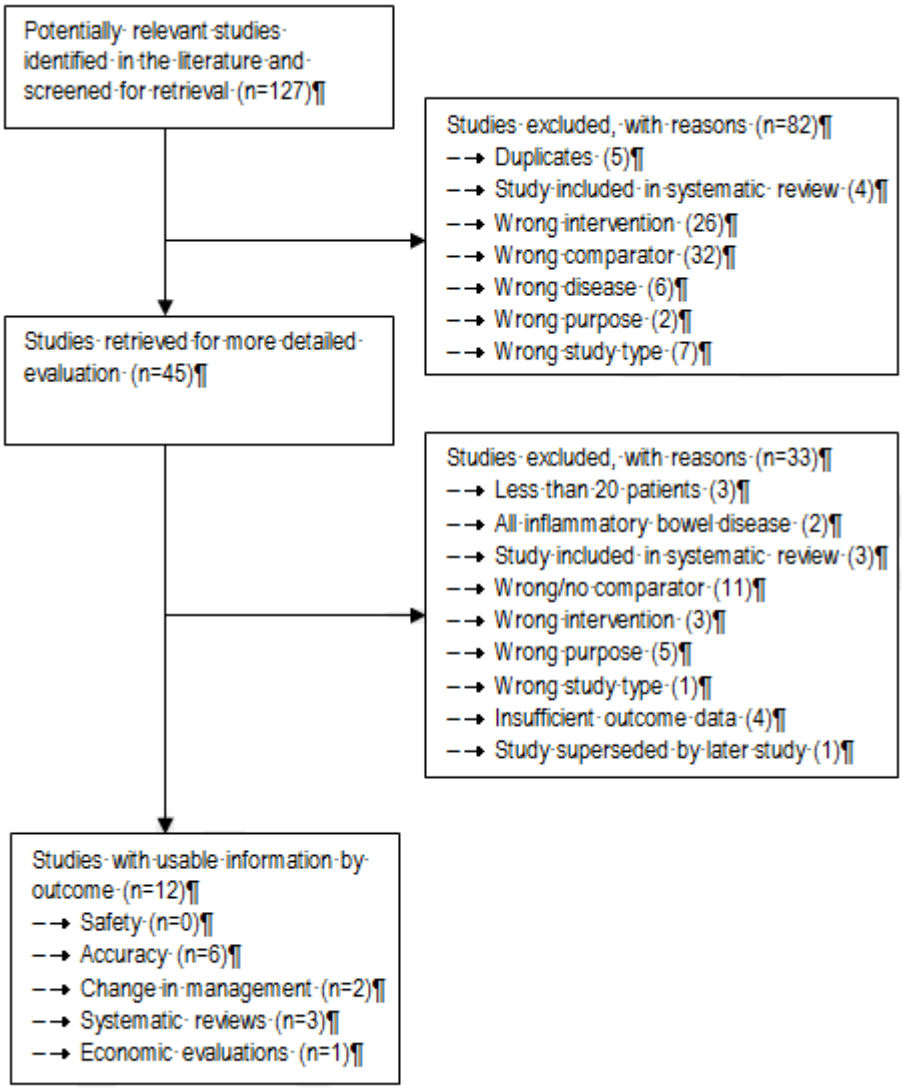
Table 7: Selection criteria for included studies

Selection criteria	Included	Excluded
Publication type	Comparative clinical studies and systematic reviews of comparative studies. Diagnostic accuracy studies and test agreement studies	Non-systematic reviews, letters, editorials, animal, in-vitro, laboratory studies, conference abstracts, pilot studies and technical reports excluded. Clinical studies or systematic reviews that have been superseded. Clinical studies that are within a systematic review selected for this review. Change in patient management studies excluded if reported outcomes are a subjective rating of physician's perceived usefulness of the test without actual changes in management plan
Patients	Studies with patients with known Crohn's disease: – including patients who are pregnant – including patients with pelvic sepsis or perianal fistulae Studies with patients with suspected Crohn's disease AND are pregnant. Studies with patients with suspected perianal Crohn's disease Studies that have selected patients with both known and suspected Crohn's disease.	Studies with <20 patients undergoing MR for the indication of interest (unless there are none). Studies that reported combined results for inflammatory bowel disease (they did not separate patients with ulcerative colitis and Crohn's disease).
Intervention/test	Magnetic resonance MR+/– enterography or MR+/– enteroclysis	Studies that did not have the primary purpose of comparing MRI with the nominated comparators for the six specified indications.
Comparators	As per the nominated indications, comparators had to be either: Abdomen CT +/– enterography CT Ultrasound (in pregnancy) Small bowel follow-through (SBFT) Endoscopy Endoanal ultrasound Surgical examination	Studies comparing MR enterography vs MR enteroclysis only Studies assessing inter-rater agreement only Studies with the following comparators: – Capsule endoscopy – Conventional enteroclysis
Outcome	Studies included if at least one of the following outcomes were reported: *diagnostic accuracy:* sensitivity and specificity (or data enabling calculation); diagnostic odds ratio or ROC curves; Q*, additional TP and FP, diagnostic yield *impact of MRI results on clinical management:* definitive treatment avoided, investigations avoided, definitive treatment instigated, overall change, type of change occurring in ≥10% patients) *patient outcomes:* Crohn's disease progression, treatment morbidity, adverse events, quality of life *prognostic value of MRI results* (patient outcomes following specific therapy selected with MR versus without MR; patient outcomes in MR+ or MR– undergoing same treatment, no change of original treatment plan of patients was altered based on a MR result)	
Language	English language articles	Non-English language articles

Search results

Quorum Flowchart

Figure 2: Summary of the process used to identify and select studies for the review



Adapted from Moher et al (1999)

Data extraction and analysis

Data were extracted using a standardised instrument designed for this review. Items extracted included characteristics of the study, objective and design, study population, type of diagnostic test, reference standard, comparator, study quality and relevant endpoints. Data were extracted by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion and by the involvement of a third reviewer if necessary. The data extraction tables are provided in Appendix D.

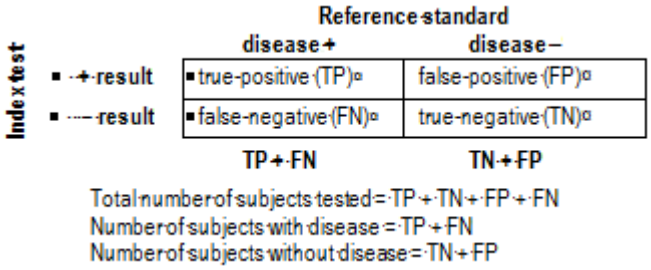
Where possible, measures of diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios) and associated 95% CIs for each test were extracted.

Measurement of test accuracy

The accuracy of a test is determined by its ability to identify the target condition compared with a reference standard test that is used as a proxy for true disease status. Subjects who test positive using the reference standard are classified as having the disease; those who test negative are classified as disease-free.

Results of the index test and reference standard for a group of tested subjects were summarised in a two-by-two table where appropriate (see Figure ~~Figure~~ 3).

Figure 3: Two-by-two table of data used to determine test accuracy



As shown, subjects who test positive for the disease of interest by both the index test and the reference standard were recorded as true-positive (TP). Subjects without the target condition who test negative by both tests were recorded as true-negative (TN). The index test result was recorded as a false-positive (FP) if it detected the target condition and the reference standard did not. A false-negative (FN) was recorded if the reference standard confirmed the target condition and the index test did not.

Sensitivity and specificity

The sensitivity of a test is the probability of a positive test in subjects with the disease of interest. The specificity of a test is the probability of a negative result in subjects without the disease. The sensitivity and specificity of a test are always considered together and vary according to the threshold used to define a positive test. Sensitivity and specificity vary according to the spectrum of disease (eg variation in disease severity) in the patient group tested. High sensitivity is particularly important if the penalty for missing a disease is high. However, high specificity is particularly important if a false-positive result can harm the patient.

Calculation

Sensitivity = TP/(TP + FN)

Specificity = TN/(TN + FP)

Positive and negative predictive values

In studies reporting the additional value of a test, only patients testing positive may receive follow-up with the reference standard. In this case the proportion of positive test results that were correct (positive predictive value (PPV)) was calculated. Where patients with discordant negative results also receive the reference standard, the proportion of negative test results that were correct (negative predictive value (NPV)) was calculated. PPV and NPV vary according to the prevalence of disease in the population.

Calculation

Positive predictive value = TP/(TP + FP)

Negative predictive value = TN/(TN + FN)

Likelihood ratio (LR)

The LR measures the probability of the test result in patients with the disease compared with those without the disease.

Calculation

Positive LR (LR+): the odds that a positive test result would be found in a patient with, versus without, a disease.

LR(+) = [TP / (TP + FN)] / [FP / (FP + TN)]

Negative LR (LR–): the odds that a negative test result would be found in a patient with, versus without, a disease.

LR(–) = [FN / (TP + FN)] / [TN / (FP + TN)]

Interpretation

- An LR of 1 indicates that the test does not provide any useful diagnostic information.
- Positive LRs >10 and negative LRs <0.1 can provide convincing evidence of diagnostic effectiveness.
- Positive LRs >5 and LRs <0.2 can provide strong evidence of diagnostic effectiveness.

However, the interpretation depends on the context in which the test is used.

Diagnostic yield

The diagnostic yield measures the proportion of MRI tests in which an (apparent) positive result or diagnosis occurred. The number of positive results and negative results are not compared against a reference standard and hence the extent of false-positives and false-negatives is unknown.

Calculation

Diagnostic yield = Number of diagnoses/Number of tests performed.

Appraisal of the evidence

Appraisal of the evidence was conducted at 3 stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review.

Stage 2: Appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the intervention.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC, 2000a).

These dimensions (Table 8) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 8: Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

Strength of the evidence

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

Level

The "level of evidence" reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results.

The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (see Table 9).

Table 9: Designations of levels of evidence according to type of research question (NHMRC, 2008a).

Level	Diagnostic accuracy [2]
I [4]	A systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]
III-2	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence
III-3	Diagnostic case-control study[6]
IV	Study of diagnostic yield (no reference standard)[11]

Table notes can be found in NHMRC (2008: 2009)(NHMRC, 2008b)

Individual studies assessing diagnostic effectiveness were graded according to pre-specified quality and applicability criteria (MSAC, 2005), as shown in Table 10.

Table 10: Grading system used to rank included studies

Validity criteria	Description	Grading System
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed to avoid bias? High quality = no potential for bias based on pre-defined key quality criteria Medium quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria	Q1 high quality Q2 medium Q3 poor reference standard poor quality or insufficient information

Quality

A structured appraisal was performed to assess the quality of all included studies. The quality of studies of diagnostic accuracy was assessed against a checklist of 11 items adapted from the QUADAS (Quality Assessment of Studies of Diagnostic Accuracy Included in Meta-Analyses) tool (Whiting et al., 2003)(see Table 11). This tool was developed by experts in the field following a systematic review of the evidence relating to sources of bias and variation relevant to studies of diagnostic test accuracy. Studies were required to meet all 11 criteria to be assessed as high quality (see details in footnote to Table 11). Only prospective diagnostic test accuracy studies were assessed as high quality. Studies that did not use a valid reference standard in all patients were classified as low quality.

Table 11: Criteria used to assess the quality of diagnostic accuracy studies – the QUADAS tool (Adapted from Whiting et al 2003).

Item	Criteria
1	Were patients prospectively recruited?
2	Were patients consecutively recruited (ie a consecutive group of patients presenting with a defined clinical presentation)?
3	Were selection criteria explicitly described (ie in enough detail to clearly define eligibility of patients and to be reproducible)?
4	Is the reference standard likely to correctly classify the target condition (valid/invalid/optimal)?
5	Did all patients receive verification using a reference standard?
6	Is the time period between reference standard, comparator and index test short enough to be reasonably sure that the target condition did not change between the tests?
7	Were MR/comparator results interpreted blind to reference standard?
8	Were reference standard results interpreted blind to MR/comparator results?
9	Were the same clinical data, including conventional imaging, available when test results were interpreted as would be available when the test is used in practice?
10	Were uninterpretable/intermediate test results reported?
11	Were withdrawals from the study explained?

MR = magnetic resonance
High quality: Yes to 1, 3, 4, 5, 9, 10; other items required to be either Yes or Unclear.
Poor quality: No/Unclear for 4, 5 or 6.
Other studies are assessed as fair quality.

Seven criteria were used to assess the quality of systematic reviews, as outlined in Table 12. For the criterion addressing heterogeneity, systematic reviews that did not undertake a meta-analysis were rated 'not applicable' (N/A), unless heterogeneity was specifically mentioned. Studies were required to meet all seven criteria to be assessed as high quality. A study with four or fewer 'Yes' or 'N/A' ratings was considered to be of low quality. Seven criteria were used to assess the quality of case series, as outlined in Table 12.

Table 12: Criteria used to assess the quality of systematic review studies (adapted from (NHMRC, 2000a) and (CRD, 2009))

Study design	Quality checklist
Systematic review	Was the research question specified?
	Was the search strategy explicit and comprehensive?
	Were the eligibility criteria explicit and appropriate?
	Was a quality assessment of included studies undertaken?
	Were the methods of the study appraisal reproducible?
	Were sources of heterogeneity explored?
	Was a summary of the main results clear and appropriate?

Statistical precision

Statistical precision was determined using statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC, 2000). Studies need to be appropriate to ensure that a real difference between groups will be detected in the statistical analysis.

Size of effect

The size of the effect needed to be determined, as well as whether the 95% confidence interval included only clinically important effects.

Relevance of evidence

The outcomes being measured in this report should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC, 2000).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC, 2008a). Five components are considered essential by the NHMRC when judging the body of evidence:

- The evidence base – which includes the number of studies sorted by their methodological quality and relevance to patients;
- The consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction ie homogenous or heterogenous findings;
- The potential clinical impact - appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test;
- The generalisability of the evidence to the target population; and
- The applicability of the evidence - integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (see Table 13). (NHMRC, 2008a).

Table 13: Body of evidence assessment matrix

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base[1]	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency[2]	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted

Component	A Excellent	B Good	C Satisfactory	D Poor
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

SR = systematic review; several = more than two studies
1 Level of evidence determined from the NHMRC evidence hierarchy – Table 6
2 If there is only one study, rank this component as 'not applicable'.
3 For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.
Source: (NHMRC, 2009)

Expert advice

An advisory panel was established to provide guidance to the health technology assessors to ensure that the assessment is clinically relevant and takes into account consumer interests. Membership of the advisory panel is provided at Appendix B.

Results of assessment

Relevant studies for assessment

The outcome of the systematic review yielded a total of 12 studies that were relevant for this assessment. A summary of these studies in provided in Table 14.

Table 14: Relevant studies included in the assessment

		Reviewed for assessment of:			
Study	Study design	Change of management	Efficacy (accuracy)	Efficacy (yield)	Economic Evaluation
Wu et al. 2013	Systematic review (17 studies)		✓		
Cheriyan et al. 2013	Retrospective, n=57	✓			
Siddqui et al. 2012	Systematic review, (4 studies)		✓		
Cipriano et al. 2012	Economic study, Markov model				✓
Sanka et al. 2012	Retrospective, n=34	✓			
Malgras et al. 2012	Retrospective, n=52	✓	✓		
Panes et al. 2011	Systematic review (68 studies)		✓	✓	
Jensen et al. 2011	Prospective, n=50		✓		
Ippolito et al. 2010	Prospective, consecutive, n=29		✓		
Schmidt et al. 2010	Prospective, consecutive, n=57		✓		
Schreyer et al. 2010	Retrospective, consecutive, n=53			✓	
Schwartz et al. 2001	Prospective, n=34		✓		

Is it safe?

No studies were identified that looked at the comparative safety of MRI for small bowel or pelvis with that of CT, SBFT or any other comparator. The safety impact of MRI in pregnancy is unknown.

There appears to be few clinical issues around patient safety with performing MRI. On its own, the test is non-invasive, does not emit ionizing-radiation and presents no chemical or bodily harm to the patient. The patient is required to lie very still on a table that is slid into a cylinder where the imaging is performed. A loud knocking sound is produced by the machine but this is not damaging to hearing and ear plugs or earphones may be used. In preparation for the MRI, the bowel must be distended with contrast enteric material, taken either orally or through a nasojejunal tube. This can be a source of discomfort to patients and their cooperation to keep immobile is needed by the radiologist to obtain a clear image. In addition, some patients can have allergic reactions to the dye although these patients have been excluded from clinical studies on MRI.

Due to being enclosed in a space for the duration of the test (approximately 30 minutes) an MRI may not be appropriate for patients experiencing claustrophobia or anxiety disorders (such as panic attacks). These patients were excluded from many of the clinical studies in this assessment. Other contraindications for MRI relate to patients with internal metal devices or other electrically, magnetically or mechanically activated devices because they may dislodge or malfunction.

In summary, for safety reasons individuals should not have an MRI if they have a:

- Brain aneurysm or haemostatic clip
- Cardiac pacemaker or cardiac defibrillator
- Cochlear implant
- Insulin pump
- Metal splinter in the eye
- Condition of claustrophobia or panic attack

Ionizing radiation of CT and SBFT

The main argument of choosing MRI over the other imaging modalities within this assessment is the advantage in not exposing patients, particularly children, to ionizing radiation. This is seen among radiologists as an important benefit in Crohn's disease, a chronic, non-curable condition that involves inflammatory relapses and therefore requires repeated testing and surveillance during the course of the patient's life. Small doses of ionizing radiation received frequently over time can lead to increased risk of cancer. Ultrasound and MRI do not emit ionizing radiation.

The effective radiation dose is a product of the radiation dose and the biological sensitivity of tissue, measured in millisieverts (mSv). Abdominal structures are more biologically active and imaging results in higher effective doses than other body parts. Susceptibility to higher effective doses is also found in younger age groups. High cumulative dose is considered >50 mSv over a 5-year period (Kroeker et al., 2011) and cumulative effective dose of >75 mSv is associated with an increased cancer risk of 7.3%. A small proportion of patients with Crohn's disease have been reported to have exceeded these benchmarks (7-15%) (Desmond et al., 2008, Kroeker et al., 2011).

The ARPANSA state that total radiation exposure should take into account background radiation exposure received from natural sources (ARPANSA, 2011). In Australia, this is reported to be 1.5mSv per year. The risk of cancer of 1 mSv of radiation is 1 in 17,000 (against the age-standardised incidence rate of 57 in 17,000) or the equivalent risk of getting cancer from smoking 100 cigarettes (ARPANSA, 2011). The relative exposures of ionizing radiation by imaging modality are: abdominal x-ray 0.7 mSv; SBFT 5.0 mSv and abdominal/pelvic CT 10 mSv. However, the effective radiation dose for each person is highly variable due to different machine settings, the amount of radioactive material used and patient metabolism.

Table 15 shows the findings of several studies that have followed patients with Crohn's disease over time and measured their radiation doses. These studies were not identified within a systematic review and therefore are not an exhaustive list of studies on this topic (Desmond et al., 2008, Kroeker et al., 2011, Peloquin et al., 2008, Sauer, 2012).

Factors found to be associated with higher radiation exposure were children (<17 years) (hazards ratio 2.1, 95%CI: 1.1 – 4.1) and those who had multiple surgeries (hazards ratio 2.7, 95%CI: 1.4 – 5.4), among others (Desmond et al., 2008).

Table 15: Annual radiation dose among patients with Crohn's disease receiving imaging tests

Study	Annual effective radiation dose (mSv)	n	Follow up time	% from CT enterography
Sauer et al. 2012	3.0 to 5.0 (3 studies)	318	3.5 to 5.2 years	-
Kroeker et al. 2011	2.8	392	5 years	75%
Peloquin et al. 2008	3.1	103	Mean 8.9 years	51%
Desmond et al. 2008	5.3	409	Mean 6.7 years	77.2%

Risk of cancer in Crohn's disease

The risk of intestinal cancer in Crohn's disease has been studied by Jess *et al.* (2005) in a meta-analysis of population-based studies. Six papers were included in the pooled analyses and the standardized incidence ratio for colorectal cancer was significantly increased in patients with Crohn's disease (1.9 (95%CI: 1.4-2.5). The authors' called for caution when interpreting this finding because the six studies included in the review were old and did not reflect current treatments or practises (Jess et al., 2005). There has since been a shift towards 'low-dose' CT techniques.

The risk of extra-intestinal cancer in inflammatory bowel disease was also been reported in a meta-analysis by Pedersen *et al.* (2010). Six population-based studies reporting on Crohn's disease were identified and involved mainly European cohorts. Overall, patients with Crohn's disease had a slightly elevated risk of extra-intestinal cancer but it was not significant; standardized incidence ratio 1.13 (95%CI: 0.89-1.40). However, patients with Crohn's disease were found to have significantly increased risks for specific site cancers: upper gastrointestinal cancer, lung, urinary bladder, and squamous cell cancer, compared with the background population (Pedersen et al., 2010).

In these two meta-analyses, the authors discussed the possible causal factors for the increased risks. Explanations provided included the nature of the disease (inflammatory), the immunosuppressive agents given to patients and the extent of cigarette smoking. They did not mention the increase risk of imaging tests as a potential source of cancer risk (Jess et al., 2005, Pedersen et al., 2010).

Is it effective?

With the exception of the economic evaluation study identified in the review, 11 studies were included in the effectiveness assessment. Effectiveness data were reported for eight primary clinical studies and three systematic reviews. Relevant data has been extracted from these studies and are provided in tables in Appendix D.

Existing systematic reviews and HTA reports

The review yielded three relevant systematic reviews and no HTA reports. Table 16 provides the characteristics and quality assessment summaries for the three systematic reviews (Panes et al., 2011, Siddiqui et al., 2012, Wu et al., 2013).

Technically, Wu *et al.* 2013 did not meet the inclusion criteria of this assessment because it does not include studies that involve within-study direct comparisons for different imaging modalities. Rather it includes diagnostic accuracy studies of MRI compared with a common reference standard (but no other imaging comparisons). However, Wu *et al.* 2013 is a high quality, recent systematic review that provides clear evidence of diagnostic performance of MRI in pooled meta-analyses of 17 studies. It also presents results of a meta-regression to assess what factors influence diagnostic performance. For these reasons, the study by Wu *et al.* 2013 was retained for assessment.

As reported by Wu *et al.* (2013), the pooled sensitivity of MRI was 87% (95%CI: 77%-93%) indicating a high ability for MRI to detect disease when it actually exists. Similarly, specificity was also high 91% (81%-96%) indicating MRI can accurately rule out Crohn's disease when it does not exist. The overall area under the receiver operator curve was 95% (95%CI: 93% -97%) (Wu et al., 2013). The review provided strong evidence of between-study heterogeneity. The most important factors associated with test accuracy were magnet strength and experience of the radiologist (in years). The applicability to the Australian population is unclear because the details of the sample profiles were minimal. The key strengths of the study include: study selection based on quality reporting, common referent test (ileocolonoscopy and histopathology) and publications were relatively recent (post 2000) and indication there was no publication bias. The main weaknesses of the evidence included whether the interpretation of pathology was blinded to the MRI introducing possible bias and overestimation of MRI accuracy.

In Siddiqui *et al.* (2012), this review specifically targeted studies assessing Crohn's perianal fistulas and compared diagnostic accuracy of MRI with endoanal ultrasound. The four studies included in the review must have compared these imaging techniques as their primary objective. The quality of the review was high and QUADAS assessment of each study was transparently reported. Meta-analysis showed that for identifying fistulas, the pooled sensitivity of MRI was 87% (95%CI: 63%-96%) and specificity 69% (95%CI: 51%-82%). For endoanal ultrasound, pooled sensitivity was identical to MRI at 87% (95%CI: 70%-95%) but lower for specificity 43% (95%CI: 21%-69%). Studies were found to be highly heterogeneous. The main weaknesses of the evidence were whether blinding occurred at the time of endoanal ultrasound and the different use of a referent (although most used surgical examination under anaesthesia)(Siddiqui et al., 2012).

Table 16: Characteristics and appraisal of included systematic reviews

Author (year)	Objective and methods	Included studies	Quality assessment of review
Wu et al (2010)	Objective: To evaluate the overall diagnostic accuracy of MRI in assessing the activity of Crohn's disease in the small bowel Method: Meta-analysis and meta-regression *Time period:* until Sept 2011 *Inclusion criteria:* studies with patients if MRI was assessed to assess active CD, studies meeting 9/14 QUADAS criteria for quality, studies applied histopathologic and ileocolonoscopy assessment as the referent standard *Outcomes:* Sensitivity, specificity, area under receiver operator curve	Suspected and established Crohn's disease: 17 retrospective and prospective studies. Studies did not provide direct comparisons (in same sample) of the different modalities, comparison with referent standard only. Test: MR Comparator: None Referent: Ileocolonoscopy and histopathologic assessment.	Quality: HIGH Was the research question specified? Yes Was the search strategy explicit and comprehensive? Yes Were the eligibility criteria explicit and appropriate? Yes Was a quality assessment of included studies undertaken? Yes Were the methods of the study appraisal reproducible? Yes Were sources of heterogeneity explored? Yes Was a summary of the main results clear and appropriate? Yes
Siddqui et al. (2012)	Objective: To undertake a systematic review to compare endoanal ultrasound with MRI for perianal fistulas in Crohn's disease. Method: Meta-analysis *Time period:*Jan1970-Oct 2010 *Inclusion criteria:* Studies that compared MR with endoanal ultrasound for patients with suspected perianal fistulas. *Exclusion criteria:* if the surgical standard was not applied. *Outcomes:* Sensitivity, specificity,	Established Crohn's disease 4 studies Test: MR Comparator: Endoanal ultrasound Referent: Examination under anaesthetic	Quality: HIGH Was the research question specified? Yes Was the search strategy explicit and comprehensive? Yes Were the eligibility criteria explicit and appropriate? Yes Was a quality assessment of included studies undertaken? Yes (QUADAS used and reported) Were the methods of the study appraisal reproducible? Yes Were sources of heterogeneity explored? Yes Was a summary of the main results clear and appropriate? Yes
Panes et al. 2011	Objective: To undertake a systematic review to compare ultrasound, CT and MRI for diagnosis, assessment of activity and complications of Crohn's disease. Methods: No meta-analysis *Time period:* Jan 1994 to Dec 2010 Inclusion criteria: Studies that compared MR ± ultrasound ± CT, had an adequate reference standard, prospective design, data allowed for calculation of sensitivity / specificity / yield *Outcomes:* Sensitivity, specificity	Suspected and established Crohn's disease 68 studies Test: MR, CT, ultrasound Comparator: Not clear (Few studies included direct comparisons of imaging tests, most were single test with a referent) Referent: Either ileocolonoscopy, capsule endoscopy, enteroscopy, surgery, pathology. No additional formal quality assessment was performed.	Quality: LOW Was the research question specified? Yes Was the search strategy explicit and comprehensive? Yes Were the eligibility criteria explicit and appropriate? Yes Was a quality assessment of included studies undertaken? No Were the methods of the study appraisal reproducible? Unclear Were sources of heterogeneity explored? N/A Was a summary of the main results clear and appropriate? No

CT = computerised tomography, MR = magnetic resonance

The systematic review by Panes *et al.* (2011) was extensive (68 studies) and included different purposes of MRI within Crohn's disease (i.e., extent of disease, severity of disease, detection of abscesses and fistulas). The review was relatively non-selective in the inclusion of studies compared with Siddiqui (2012) and Wu (2013) reviews. Few studies included comparative assessments across different imaging modalities. Quality assessment of the included studies and pooled analyses were not undertaken by the authors. Appendix D provides full details of the different outcomes by MRI purpose.

For the detection of Crohn's disease activity in four studies, the range of sensitivity estimates for MRI were 80-91% and specificity 67-100% compared with CT sensitivity 60-95% and specificity 80-100% (Panes et al., 2011). The review was assessed as low quality due to the unclear methods used, the lack of quality assessment of the included studies, heterogeneity of the studies and lack of summary of main results. Importantly, the studies included a range of referent standards in which to measure accuracy making comparisons difficult.

Direct evidence

The current review did not identify any studies comparing the health outcomes of patients evaluated with MRI for small bowel and perianal fistulising suspected or known Crohn's disease. In the absence of direct evidence for the effectiveness of MRI, the evidence of diagnostic accuracy, change in management and the expected benefits of changes in treatment on health outcomes are presented using a linked evidence approach on the value of MRI in these indications.

Indirect evidence

A total of eight primary clinical studies met the inclusion criteria for this review (Cheriyan et al., 2013, Ippolito et al., 2010, Jensen et al., 2011, Malgras et al., 2012, Sanka et al., 2012, Schmidt et al., 2010, Schreyer et al., 2010, Schwartz et al., 2001), six diagnostic studies and two 'change of management' studies.

Is it accurate?

For the six diagnostic accuracy studies, summaries of the main features, quality assessment and key results are provided in Tables 13 and 14. These studies provide diagnostic performance outcomes as additional evidence to the studies captured within the three systematic review studies in this assessment (Panes et al., 2011, Siddiqui et al., 2012, Wu et al., 2013).

As shown in Table 17, all studies were conducted in Europe and there were no Australian studies meeting the eligibility criteria. All studies involved patients with established Crohn's disease with similar mean age (34-42 years) and range (18-70 years) but different gender proportions with the proportion of males ranging from 26% to 69%. Four studies compared MR enterography with CT enterography (Ippolito et al., 2010, Jensen et al., 2011, Schmidt et al., 2010, Schreyer et al., 2010), one compared MR enterography with CT enterocylsis (Malgras et al., 2012) and one pelvic MR enterography with endoanal ultrasound and surgical examination (Schwartz et al., 2001).

Only one high quality study was included (Jensen et al., 2011) and one further study was judged as medium quality (Schmidt et al., 2010). Two studies represented NHMRC Level II evidence (Jensen et al., 2011, Schwartz et al., 2001)while the remaining studies were Level IV evidence (the lowest NHMRC level). Studies were categorised as low quality because:

- They had no referent standard and were test agreement studies;
- There was little description of the inclusion or exclusion criteria;
- Blinding between the index test and comparator was generally not performed. Blinding between tests and referent standard not undertaken in Schmidt *et al.* (2010);

- The sample sizes were small; and
- It was unclear if the patients were selected consecutively or non-consecutively and therefore studies may have selection bias.

An additional limitation of the studies was partial reporting of outcomes data (i.e. insufficient data for a 2 x 2 table). For example sensitivity estimates were available for two studies (Malgras et al., 2012, Schwartz et al., 2001) but specificity was not reported or calculable from the available results.

As shown in Table 18, the sensitivity of MRI was high and consistent with the results from the systematic reviews (range 74% to 100%). Similarly, CT also produced high sensitivity across the studies (range 83% to 100%). With the low and high confidence intervals of these estimates overlapping, the diagnostic accuracy of MRI and CT is considered equal for sensitivity in assessing extent of disease, complications and perianal disease.

The specificity of MRI was also high for the studies reporting this outcome (range 80% to 100%) but similar compared with CT (range 67% to 100%).

The study by Jensen *et al.* (2011) assessed as high quality, and having the least chance of biased outcomes, found sensitivity and specificity results at the lower end of the overall range across the studies. Statistical analysis showed that the sensitivity and specificity of MR enterography was not significantly different from CT enterography. Of concern is the specificity of MRI 80% (95% CI: 44%, 98%) with a negative predictive value of 47% (95%CI: 23%, 72%) and slightly lower than for CT for detection of disease extent (Jensen et al., 2011). MRI and CT therefore do not discriminate negative test findings well in those without disease. The implications in terms of patient management mean that treatments may not be offered in those patients with disease but who received a negative MR test.

No studies were found specifically assessing MRI in pregnancy. Studies that reported exclusion criteria excluded women who were pregnant or lactating due to the comparisons involving MRI with CT. CT is contraindicated for women who are pregnant.

No studies were found comparing extent of disease or complications of disease using the comparator small bowel follow through.

Table 17: Characteristics and appraisal of 6 included accuracy studies

Author (year) Setting Time period	N	Test comparison	Population	Study design	Quality and applicability
Malgras (2012) France Single centre	52	MR enterography vs CT enteroclysis	• Patients with known CD referred for surgery • Mean age 37 years, 56% male • Prior tests: videocolonoscopy	Study design: Retrospective Reference standard: Surgical exam + pathology Outcomes: Accuracy, diagnostic yield	NHMRC level of evidence: IV Comparison: CX Applicability: P1 Quality: Poor
Jensen (2011) Denmark Multi centre	50	MR enterography vs CT enterography	• Patients with known CD • Median age 39 years, 26% male • Prior tests: endoscopy, radiology, surgery	Study design: Prospective Reference standard: Surgical exam, ileoscopy or endoscopy Outcomes: Accuracy, diagnostic yield	NHMRC level of evidence: II Comparison: C1 Applicability: P1 Quality: High
Ippolito (2010) Italy Single centre	29	MR enterography vs CT enterography	• Patients with known CD • Age range 14-70 years, 69% male • Prior tests: biopsy confirmed CD	Study design: Prospective, consecutive Reference standard: none Outcomes: Diagnostic yield,	NHMRC level of evidence: IV Comparison: C1 Applicability: P1 Quality: Poor
Schmidt (2010) Italy Single centre	57	MR enterography vs CT enterography	• Patients with known CD • Mean age 33.5 years, range 17-69 years • Prior tests: NS	Study design: Prospective Reference standard: Composite of surgery, endoscopy, long-term follow up Outcomes: Accuracy, diagnostic yield	NHMRC level of evidence: IV Comparison: CX Applicability: P1 Quality: Medium
Schreyer (2010) Germany Single centre	53	MR enterography vs CT contrast enhanced	• Patients with known CD presenting to emergency department • Median age 37 years, range 18-73 years • Prior tests: NS	Study design: Retrospective Reference standard: none Outcomes: Diagnostic yield	NHMRC level of evidence: IV Comparison: C1 Applicability: P2 Quality: Poor
Schwartz (2001) USA Single centre	34	Endoanal ultrasound vs MRI pelvis vs surgical exam	• Patients with known CD and suspected perianal fistulas • Mean age 36 years, range 18-70 years • Prior tests: No other pre-operative imaging	Study design: Retrospective Reference standard: Combined endoanal ultrasound, MRI pelvis, surgical exam Outcomes: Accuracy, diagnostic yield	NHMRC level of evidence: II Comparison: C1 Applicability: P1 Quality: Poor

Abbreviations: AU = abdominal ultrasound, CD = Crohn's disease, CT = computed tomography, MRE = magnetic resonance imaging with enterography, MRI = magnetic resonance imaging, SBFT = small bowel follow-through

Table 18: Summary of key results from diagnostic studies and systematic reviews

Study	N	Diagnostic Yield		Sensitivity % (95%CI)		Specificity % (95%CI)	
		MRE	Comparator	MRE	Comparator	MRE	Comparator
Wu (2013)	725	-	-	87% (95%CI: 77%, 93%)	n/a	91% (95%CI: 81%, 96%)	n/a
Siddiqui (2012)	113	-	-	MRI 87% (95%CI: 63%, 96%)	Endoanal US 87% (95%CI: 70%, 95%)	MRI 69% (95%CI: 51%, 82%)	Endoanal US 43% (95%CI: 21%, 69%)
Panes (2011)	4 studies[1]	-	-	Range 80-91%	CT Range 60-95%	Range 67-100%	CT Range 80-100%
Malgras (2012)	52	-	-	100% (95%CI: 92%, 100%)	CT enteroclysis 93% (95%CI: 82%, 99%)	Not calculable	Not calculable
Jensen (2011)[2]	50	-	-	74% (CI: 57%-88%)	CT enterography 83% (CI: 66%-93%)	80% (CI: 44%-98%)	CT enterography 70% (CI: 35%-93%)
Ippolito (2010)	29	-	-	100%	CT enterography 100%	100%	CT enterography 100%
Schmidt (2010)	57	-	-	84%	CT enterography 93%	91%	CT enterography 67%
Schreyer (2010)	53	49/53 (92%)[3]	CT enterography 49/53 (92%)	-	-	-	-
Schwartz[4](2001)	34			26/30 (87%) (CI 69%-96%)	Endoanal US 29/32 91% (CI 75%-98%) Surgical exam 29/32 91% (CI 75%-98%)	Not calculable	Not calculable

CD= Crohn's disease, MRE= magnetic resonance enterography, US= ultrasound, SBFT=small bowel follow-through

1. Results are presented for 4 studies for detection of activity in CD (Fiorino 2011, Lee 2009, Siddiki 2009, Low 2000)
2. Results are for detection of activity in CD PPV MR: 93% (CI: 77%-99%) CT 91% (CI: 75%-98%) NPV MR: 47% (CI: 23%-72%) CT NPV: 54% (CI: 25%-81%)
3. Terminal ileum disease activity
4. MRI pelvis

Does it change patient management?

Two studies were identified with the primary purpose of investigating the change in patient management using MRI for patients with known Crohn's disease (Cheriyan et al., 2013, Sanka et al., 2012).

The study by Cheriyan (2012) involved 57 patients with small bowel Crohn's disease and mean disease duration of 9.5 years. There was no referent for the MRI and a description of current management options for the participants was not provided. A total of 50/57 patients had abnormal MR enterography (i.e., 5 stricturing, 17 active, 14 both active and structuring) and most of these 42/50 had a change in management, 22 (53%) had medical intervention and 20 (47%) underwent surgery. The authors concluded that MRI had a substantial clinical impact on patient management (Cheriyan et al., 2013). The results should be viewed with caution due to the descriptive nature of the study and poor overall quality (see Appendix D)

In a retrospective paediatric study by Sanka (2012), 34 children were evaluated for change in management for small bowel Crohn's disease. Nine children had normal MR enteroclysis and were either discharged (n=8) or management did not change (n=1). After MR enteroclysis, 13 patients commenced azathioprine, methotrexate, adalimumab or infliximab and five patients underwent surgery (Sanka et al., 2012). As for Cheriyan (2012), the results were descriptive and had a number of limitations including reporting the medical management at baseline (Appendix D).

A notable limitation of the two studies above is that the current management of Crohn's disease before MRI was undertaken was not stated and therefore the transitions between pharmacological or other treatments are not clear. The claim that earlier or more appropriate treatment, or the avoidance of surgery, or the cessation of expensive drug therapy, is not supported by these two studies.

No studies were identified involving patients with perianal fistulising Crohn's disease that addressed change or response in therapy.

Does change in management improve patient outcomes?

No comparative studies were identified in the systematic review that reported on improvements to patient outcomes as a response to MRI in Crohn's disease.

Other relevant considerations

Ongoing trials

A number of trials are currently underway which are related to this application but not directly. These include:

- NCT01881490 ImageKids Study: Developing the Pediatric Crohn's Disease Intestinal Damage Score NCT00204165 (PECDID) & the Pediatric MRE-Based Activity Index (P-MECAI)
- Comparison of MR Enteroclysis and MRI With Per Oral Contrast Using a 6 % Mannitol Solution.
- NCT01183403 CE-U and MRE to Predict the Efficacy of Anti-TNF Therapy in Crohn's Disease (CREOLE)
- NCT01593462 Comparative Effectiveness of MR Enterography (children, currently recruiting)
- NCT01671579 Comparison of Bowel Ultrasound & MR Enterography in the Follow-up of Previously Diagnosed Pediatric Small Bowel Crohn's Disease (currently recruiting)
- NTR2201 Evaluation of dynamic MRI with T1-maps correlated with histopathology in patients with crohn's disease. (Netherlands, recruiting)

Expert opinion

During this assessment a number of issues were raised by HESP experts. One relates to the age of the MRI machines currently in existence in Australian hospitals. Some of these machines are ageing and new advances in fast scanning techniques etc have improved imaging quality.

Experts have expressed the view that MRI would be used more widely if it were available in all hospitals and patients did not have to pay out-of-pocket expenses. Furthermore, they suggested that SBFT is virtually superseded by CT enterography; the current use of SBFT is very low. Clinicians would be more likely to refer their patients to a location where MRI or CT was available than to use SBFT.

Consumer implications and other considerations

Consumer survey responses for this item were positive and supportive and note that potential disadvantages are few (only that some patients experience claustrophobia with MRI). In addition, in order to complement the introduction of MRI to diagnose small bowel Crohns disease, survey responses also feel that funding faecal calprotectin as a non-invasive marker of gut inflammation needs to be considered.

From a patient perspective the main differences between MRI and CT scans are summarised in Table 19. These relate to greater cost for MRI, lower comparative access to MRI, time burden of MRI and reduction in ionizing radiation. This kind of information is readily available to consumers via imaging company websites.

Table 19: Patient-relevant differences in MRI or CT scans in Australia

CT - Computed Tomography	MRI - Magnetic Resonance Imaging
Ionising radiation	No ionising radiation
Unsafe in pregnancy	No known risk but avoided in pregnancy
Scans takes around 5-10 minutes	Scans take 30 minutes or longer
Cheaper: • Part rebate from Medicare • Some practices bulk billing	Expensive: • Few rebates from Medicare • Few practices bulk billing
Hundreds of locations in Australia	Dozens of locations in Australia
Metal implants OK	Metal implants potentially dangerous
Cardiac devices mostly OK	Cardiac devices may malfunction
Cochlear implants usually OK	Cochlear implants may be affected
Insulin pumps usually OK	Insulin pumps may malfunction

Source: http://www.medscans.com.au/info/ct-vs-mri.html

What are the economic considerations?

Summary of the evidence

A summary of the evidence for assessing the diagnostic accuracy, safety and subsequent patient consequences of MRI compared to various comparators in this application are provided in Table 20.

Table 20: Summary of evidence for MRI versus Comparator(s)

		Diagnostic Accuracy			
Proposed indication of MRI	Comparator	Sensitivity	Specificity	Patient Benefits	Safety outcomes
Small Bowel					
Extent of CD	SBFT, CT	Equivalent to CT	Equivalent to CT	No evidence	No evidence
Complications in CD	SBFT, CT	Equivalent to CT	Equivalent to CT	No evidence	No evidence
Pregnancy	Ultrasound	No evidence	No evidence	No evidence	No evidence
Change in therapy	SBFT, CT	No evidence	No evidence	No evidence	No evidence
Perianal/Fistulising					
Pelvic sepsis and fistulas	Surgical exam or endoanal ultrasound	Equivalent	Equivalent/ superior	No evidence	No evidence
Change in therapy	Endoanal ultrasound	No evidence	No evidence	No evidence	No evidence

CD= Crohn's disease, CT = Computed Tomography, MRE= magnetic resonance enterography, US= ultrasound, SBFT=small bowel follow-through

Small bowel CD: The evidence suggests that MRI is equivalent to CT for detecting the extent or complications in patients with known Crohn's disease in the small bowel. There were no comparative studies to provide evidence of MRI for diagnostic accuracy in pregnancy or for assessing change in therapy. No comparative studies were found for assessing use of MRI and linking this to patient benefits or patient safety outcomes. On the basis of the overall evidence base for the proposed MR indications for small bowel in this application a full cost-utility analysis is not warranted.

Perianal fistulising CD: For evaluating the presence of pelvic sepsis and fistulas, MRI was assessed as being equivalent to endoanal ultrasound for sensitivity and superior for specificity. However, the improvement in specificity for MRI was not tested statistically and the specificity for both CT and MRI was considered low. No comparative studies provided evidence of MRI for assessing change in therapy. No comparative studies were found for assessing use of MRI and linking this to patient benefits or patient safety outcomes. On the basis of the evidence for MRI for perianal fistulising CD, a cost-effectiveness analysis is appropriate for assessing pelvic sepsis and fistulas.

Overview of the economic considerations

The economic considerations appropriate to this application include:

1) An assessment of the cost-effectiveness analysis of MRI for pelvic sepsis and fistulas; and

2) An assessment of the financial implications of the proposed reimbursement of MRI for all the proposed indications.

Published economic literature

In order to inform the cost-effectiveness study, a review of the literature for relevant economic studies was undertaken at the time of the clinical effectiveness data search. Figure 2 and Table 7 provide full details of the literature search.

One published economic evaluation was identified as relevant to this application (Cipriano *et al.* 2012) and more specifically to MRI small bowel Crohn's disease. This study compared MR enterography with CT enterography for the routine monitoring of those with established Crohn's disease. The study was US-based and costs were reported in US dollars and reflect US prices and resources. A Markov model was developed with monthly cycles and from age 20 onwards with lifetime duration. The model was tested using different frequencies of MRI testing (once annual, twice annually, once biannually etc) and included MRI or CT only in addition to MRI and CT switching after a certain number of years. The main outcomes were quality-adjusted life years and costs (Cipriano et al., 2012).

The main patient-relevant outcome was the reduction in cancer risk attributed to MRI. The increase in cancer risk was attached to each CT scan and aggregated additively over time. The model synthesized cost, natural history paramaters, utilities, and radiation/cancer risk estimates using published literature. For example the effective radiation dose for CT scan was assumed to be 16 mSv and tested between 12 to 25 mSV in sensitivity analyses. The link between effective dose and increased risk of cancer in Crohn's disease was based on a meta-analysis (Pedersen et al., 2010). The Markov model was validated and checked according to the increased risk of cancer across various sites (e.g., kidney, colon, stomach, lung etc). Two important issues relating to the analysis included:

1. The model assumed equivalent diagnostic accuracy and consequently equivalent patient management across the CT and MRI options; and
2. The authors found no prospective studies specifically linking CT-radiation exposure to cancer mortality and concluded that randomized controlled trials on this topic were probably not feasible.

Using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau et al., 2013), the transparency and comprehensiveness of the reported model was assessed. These findings are reported in Appendix F. Overall, the study methods and reported results were of high quality, subject to some caveats and necessary assumptions in the absence of evidence. Full details of the synthesized evidence base and analytical decisions were provided in an online supplementary file.

The economic model found that the incremental cost effectiveness ratios for an annual MRI scan to replace CT scans were; (USD 2009) $54,345 per QALY until age 30, $65,494 per QALY until age 40 and $124,217 per QALY until age 60. The incremental QALYs were marginal from MR until age 30 and ranged from 0.14 to MR until 40 years and 0.23 to MR until age 60 (Cipriano et al., 2012).

Unit costs for each MR enterography were US$2155 and US$1304 for CT enterography. These prices are 3-fold higher than Australian prices. In sensitivity analyses, if the difference between MR enterography and CT enterography was more than $600 per scan, the cost effectiveness ratio was greater than US$100,000 per QALY. The cost of MR is a key driver of cost-effectiveness in this long-term model. Using the same model with Australian costs, where the cost of the comparable MRI is $627.50 and CT, $480.05 and a price differential of $147, would result in a greatly improved cost-effectiveness ratio.

However, the applicability of the findings of Cipriano *et al.* (2012) to the Australian setting are unclear and may not be especially relevant given the differences in cancer epidemiology health care systems and resource use between Australia and the US. Nonetheless, this study provides a useful contribution to the potential downstream consequences of MR as a replacement for CT in a careful and comprehensive health economic report.

Economic evaluation

An economic evaluation was undertaken to model the costs and effects of superior specificity of pelvic MRI for detection of fistulas/abscesses in fistulising Crohn's disease.

Overview

A linked approach was taken whereby a higher specificity of MRI compared with endoanal ultrasound lead to fewer false negatives and potentially more appropriate management. The evidence supporting this link for an altered clinical course of disease is not firmly supported by the evidence and therefore this analysis should be viewed with caution and is considered hypothetical.

The key parameters of the model are provided in Table 21 together with the sources. The structure of the model is provided in Figure 4.

Justification of model parameters and assumptions

A decision-analytic model was constructed and all analyses were performed in TreeAge Pro 2013 software. The model was a simple representation comparing the two test strategies and draws on evidence from the literature. In the absence of long-term clinical data, the model duration was 12 months. Although Crohn's disease is incurable and chronic in nature, the flare-ups and complications that arise need to be attended to quickly and in acute care settings. We therefore made assumptions regarding only the potential short-term consequences of testing performance on early healthcare resource use and patient quality of life (utility values). The main outcomes of the model are costs and QALYs over 12 months. Due to the short duration, discounting costs or QALYs was not necessary.

Schwartz *et al.* (2004) referenced several studies that have shown when abscesses and fistulas are not detected, it can result in recurrent fistulas or convert simple fistulas to complex ones with significantly reduced healing rates (Schwartz and Herdman, 2004). An assessment of these individual studies did not provide clear figures on the extent of recurrence in failed imaging studies. Others state that repeated surgeries and higher medical costs are accrued for patients with more severe Crohn's disease (Yu et al., 2008). It is possible that simple fistulas that go undetected during imaging will cause a delay in

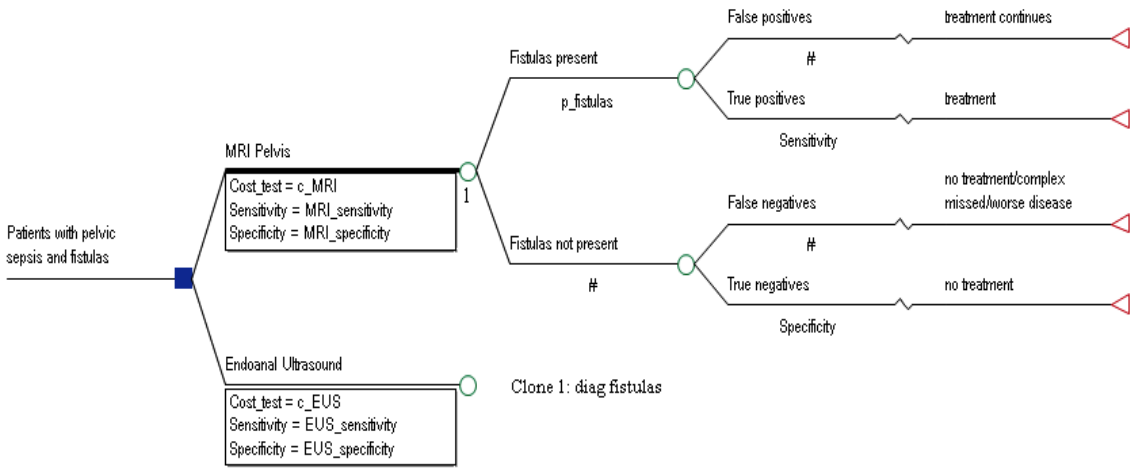
appropriate treatment (usually surgery combined with medical treatment), ongoing patient discomfort and increased testing and resources for symptom relief (Schwartz and Herdman, 2004). Therefore, it was assumed that a false negative finding on either MR or endoanal ultrasound would result in a proportion of these patients (30%) accruing higher costs for additional tests and examinations and possibly repeat surgical procedures for complex or recurrent disease. This proportion was tested between 20% and 50%. We also tested the scenario of $0 additional cost for false negatives. Recurrence is especially high for complex perianal fistulas and has been reported at 53% at 14 months (Makowiec et al., 1997).

Table 21: Parameters used in the decision-analytic model for pelvic MRI versus CT for detection of fistulas/abscesses in fistulising perianal Crohn's disease

Description	Base	Low	High	Distribution	Source
Model duration	12 months	-	-	-	
Discounting	n/a	-	-	-	
Probabilities					
MRI specificity	0.69	0.51	0.82	Beta α=22.90 β=10.29	Siddiqui 2012
MRI sensitivity	0.87	0.63	0.96	Beta α=13.01 β=1.94	Siddiqui 2012
EUS specificity	0.43	0.21	0.69	Beta α=6.60 β=8.76	Siddiqui 2012
EUS sensitivity	0.87	0.70	0.95	Beta α=21.51 β=3.21	Siddiqui 2012
Probability of perianal fistula in one year	0.12	0.09	0.25	Beta α=5.87 β=43.02	Ng 2013
Proportion of surgery requiring repeat surgery for recurrence	0.3	0.20	0.50	Beta α=18.67 β=43.56	Assumption
Costs					
Cost of pelvic MRI	$403.20	$342.72	$463.68	Normal μ=403.20 σ=60.48	Proposed, ±15%
Cost of endoanal ultrasound	$55.65	$0	$55.65	Normal μ=55.65 σ=8.35	MBS item #55014
Cost of surgery	$3878	$3296	$4460	Normal μ=3878 σ=581.40	AR-DRG item #J09Z
Cost of surgery if false negative	c_surgery*(1+p_repeat_surg)	$0	$7756	-	Assumption
Utilities					
Utility of CD in person with true positive	0.815	0.725	0.955	Beta α=22.90 β=10.29	Cipriano 2012
Utility of CD when false negative or false positive occurs	0.725	0.625	0.825	Beta α=1.83 β=0.70	Cipriano 2012
Utility of CD in person with true negative	0.955	0.815	1.000	Beta α=12.16 β=0.57	Cipriano 2012

CD= Crohn's disease, CT = computer tomography, EUS = endoanal ultrasound, MRI= magnetic resonance imaging

Figure 4: Diagram of decision-analytic model for pelvic MRI versus CT for detection of fistulas/abscesses in fistulising perianal Crohn's disease



Costs were assigned to perianal surgery, ultrasound and MRI using MBS scheduled fees, the proposed MBS fee for MRI and the latest AR-DRG public hospital cost weights for perianal procedures. Utility values were derived from Cipriano 2012 which sourced EQ-5D utility values (for patients with Crohn's disease) from the Medical Expenditure P Survey in the US. A range of values were reported around the mean 0.81 (95%CI: 0.725, 0.955) (Cipriano et al., 2012). An assumption was made to use 0.81 for positive tests with accompanying prompt and effective treatment, 0.725 for false negative or false positive tests and 0.955 for true negatives where patient quality of life may be relatively high. These values were tested generously in sensitivity analyses.

It is assumed that medical therapies and other resources already used by individuals will be equal across the imaging strategies and these were omitted from the model. It is also assumed that individuals will be those of a demographic and clinical description of those from the meta-analysis of Siddiqui *et al.* (2012) on where the key sensitivity and specificity MRI data are derived.

Base case and sensitivity analyses

A mean expected value analysis was performed. The costs and QALYs were aggregated across the branches to produce mean outcomes. Sensitivity analyses were undertaken as warranted by the high level of assumptions made in the data parameters. One-way sensitivity analyses were undertaken for all variables using the 95% confidence intervals for the high and low values, where available, or estimates were assigned to reflect wide variation in the base value (Table 21). Probability sensitivity analyses were undertaken to vary all variables simultaneously and 1000 Monte Carlo simulations were produced. Beta distributions were assigned for probabilities and utilities and normal distributions were used for costs (due to expected stability in the cost estimates).

Results of the cost-utility analysis

The results of the cost-utility analyses are presented in Table 22.

Table 22: Results of the cost-utility analysis of MRI and endoanal ultrasound for detecting perianal fistulas in Crohn's disease (12 months)

Base	Mean Costs	Mean QALYs	ICER
MRI	$2243	0.87	
Endoanal ultrasound	$3049	0.82	
Incremental outcomes	-$806	0.05	Dominant
One-way sensitivity analyses (selected)	Incremental Costs	Incremental QALYs	ICER
Cost of surgery if false negative			
- Low $0	$348	0.05	$6,604
- High $7756	-$1427	0.05	Dominant
Utility of CD in person with true negative			
- Low 0.815	$806	0.02	Dominant
- High 1.00	$806	0.06	Dominant
Endoanal ultrasound specificity			
- Low 0.21	-$1782	0.10	Dominant
- High 0.69	$348	0.00	$3,476
MRI specificity			
- Low 0.51	-$7	0.02	Dominant
- High 0.82	-$1383	0.08	Dominant
Utility of CD when false negative or false positive occurs			
- Low 0.625	$806	0.08	Dominant
- High 0.825	$806	0.03	Dominant
Probability sensitivity analysis			
Incremental outcomes	-$795	0.05	Dominant (95% CrI: dominant, $508,192)

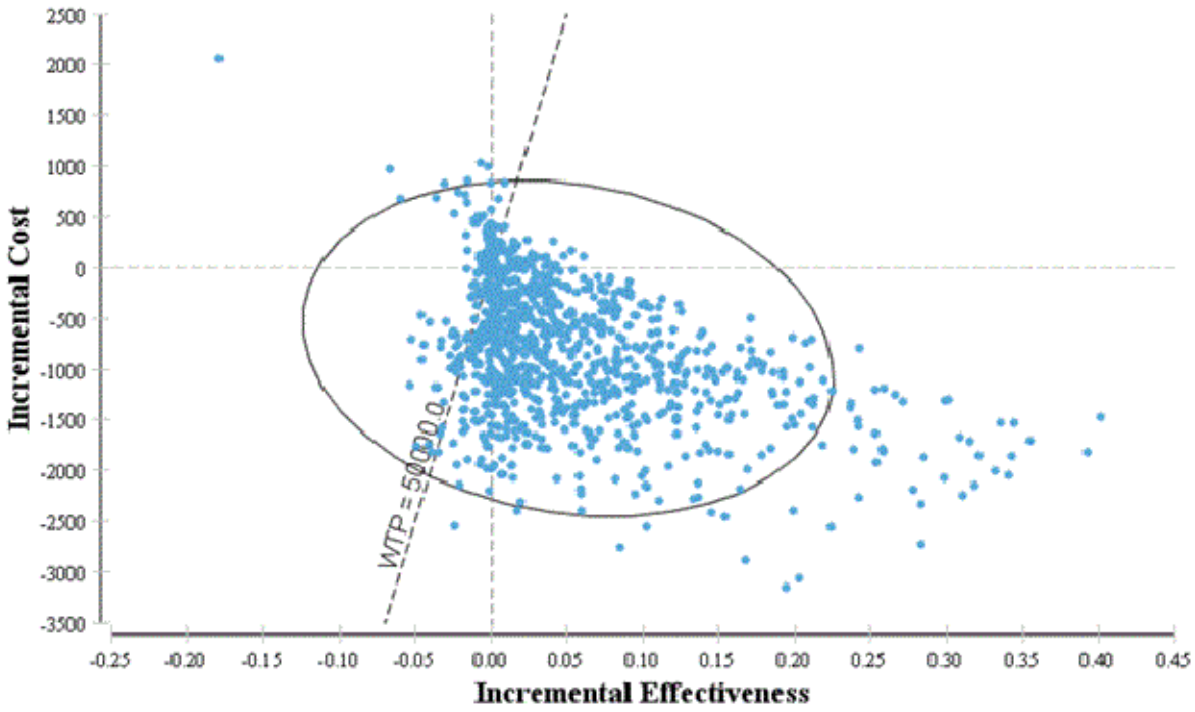
CD = Crohn's disease, CrI = Credible Interval (interpreted like a Confidence Interval but based on a ranking order and excluding the top and bottom 2.5% of simulations), MRI = Magnetic resonance imaging

In the base case analysis, the mean cost of MRI was lower than endoanal ultrasound (by $806) meaning MRI could potentially produce cost-savings over 12 months. The corresponding QALYs were slightly higher in the MRI strategy compared with endoanal ultrasound (by 0.05). Therefore, MRI could be considered superior to endoanal ultrasound as it is less costly and more effective, based on the model assumptions.

The results of the model were most influenced by the cost of surgery if there was false negative finding, the utility score with true negative, the specificities of endoanal ultrasound and MRI and the utility scores of false negatives or false positives. However, even when using wide variation to these values in the sensitivity analyses (e.g. $0 for resource impact of a false negative result), they did not change the finding that MRI would be a cost-effective choice.

In the probabilistic sensitivity analysis, the incremental cost and incremental QALY pairings from 1000 simulations are illustrated in (Figure 5). The figure illustrates that 78.6% of simulations would be cost-effective at $50,000 per QALY and in the vast majority, (74%) MRI would be cost-saving compared with endoanal ultrasound. However, this favourable outcome for MRI is volatile to the choice of costs for perianal surgery) for patients with false negative results from MRI. The model is also highly dependent on the quality of life impact of the various test results and immediate consequences on clinical treatment. These appear to be the main drivers of the model as per the one-way sensitivity analyses.

Figure 5: Incremental cost effectiveness scatterplot of MRI vs CT in perianal Crohn's disease



Interpretation of diagram: the dots in the top right quadrant below the diagonal willingness to pay (WTP) line and the dots in the bottom right quadrant – together are considered cost-effective outcomes. The proportion of these dots to all dots is 78.6%.

Conclusion: MRI for fistulsing perianal Crohn's disease for the extent of abscesses and fistulas is cost-effective compared with CT. The likelihood of MRI being cost effective relative to CT is 78.6%, subject to the parameters and assumptions made in the model.

Costing

In order to provide financial estimates of MRI for the proposed indications in this application, an assessment of the epidemiology and the natural history of Crohn's disease is required. The financial estimates presented here take an epidemiological approach.

Australian epidemiological studies

Natural history studies of Crohn's disease in Australian populations are important information for the economic assessments in this application. A brief literature search uncovered only two studies reporting epidemiological information for Australians with Crohn's disease within larger cohorts of inflammatory bowel disease (Ng et al., 2013, Wilson et al., 2010). A summary comparing these key outcomes are provided in Table 23. Figures for Ng *et al.* (2013) apply to the Australian cohort (as a subset of the entire sample) unless otherwise stated.

Table 23: Australian epidemiological studies on inflammatory bowel disease (IBD)

	Wilson et al. 2010	Ng et al. 2013
Time of case ascertainment	2007/2008 (12 months)	2011/2012 (12 months)
N (IBD)	76	71 (Australia only)
Crude annual incidence Crohn's disease (95%CI)	17.4 per 100,000 (95%CI: 13.0-23.2)	14.0 per 100,000 (95%CI: 10.1-18.9)
Crude annual incidence ulcerative colitis (95%CI)	11.2 per 100,000 (95%CI: 7.8-16.1)	7.3 per 100,000 (95%CI: 4.6-11.1)
% of Crohn's to IBD	45/76 (59.2%)	59.1%[1]
% of Crohn's to ulcerative colitis	45/29 (155.2%)	191.0%[1]
Median age	34 years	34 years[2]
Age range	9-76 years	5-81[2]
% females (IBD)	43/76 (56.6%)	52.4%
Crohn's disease phenotype	22% terminal ileum or small bowel 27% isolated colon 24% colon and small bowel	31% small bowel 24% colonic 45% ileocolonic 5% upper gastrointestinal
Disease behaviour	93% Inflammatory 4.5% Stricturing 1.5% Penetrating	88% Inflammatory 10% Stricturing 2% Penetrating 12% Perianal 12% Stricturing and perianal

1. Based on crude annual incidence rates
2. Applies to the whole sample of study n=419 new IBD cases

Both studies involved detailed and validated case ascertainment in the Geelong region of Victoria, Australia with a population of 300,000. Geelong has well-defined boundaries and is relatively geographically isolated. It has one central pathology and endoscopy centre. It is also representative of the wider Australian population according to many socio-demographic variables. The study by Ng *et al.* 2013 was undertaken 4 years after Wilson and show similar incidence rates albeit slightly lower.

Prevalence estimates in Crohn's disease are difficult to assess because they require knowledge of historical incidence data. However, two separate reports have estimated the prevalence of inflammatory bowel disease at 75,000 (PricewaterhouseCoopers Australia, 2013) and 65,000 (Wilson et al., 2010).

Eligible population

Table 24 provides a list of values and their sources considered in the financial analysis relating to the number of patients in Australia potentially eligible for the proposed MRI indications.

Table 24: Estimates and sources to calculate eligible population

	Base	Sensitivity		Source (s)
Annual estimates	Estimate	Low	High	
Estimated Australian population	23,301,991	-	-	ABS #3101.0 Australian Demographic Statistics
Growth rate in population per year	1%	-	-	ABS #3222.0 Population projections
Incidence rate of Crohn's disease - crude per 100,000 individuals	14.0	10.1	23.2	Ng 2013, Wilson 2010
Prevalence of IBD (cases)	75,000	65,000	85,000	Price Waterhouse 2013, Wilson 2010
% of IBD diagnosed as Crohns	59%	-	-	Wilson 2010 based on incidence figures
Estimated growth rate in Crohn's disease (annual)	2%	0%	5%	Assumption, rapid growth reported in many international studies
% of small bowel Crohn's disease	46%	31%	65%	Wilson 2010, Ng 2013
% of perianal fistulising Crohn's disease	12%	8%	16%	Ng 2013, DAP estimates during first year, 1% thereafter
% pts with CD presenting for extent of CD small bowel	100%	80%	-	Of all incident cases, diagnose and assess extent, Assumption
% pts with CD presenting with complications small bowel	20%	15%	25%	Of all prevalent cases, Gollop 1988 (19%)
% pts who are pregnant and suspected CD	0.2%	-	-	Assumption, known to be a very small number
% pts with CD for assessment of therapy small bowel	20%	15%	25%	Of all prevalent cases, trials indicate this difference in response rate to therapy
% pts with CD for suspected perianal CD	100%	80%		Of all perianal CD cases
% pts with CD for assessment of therapy perianal fistulising	50%	40%	60%	Of all perianal CD cases

CD= Crohn's disease, IBD = inflammatory bowel disease, pts = patients

The current use of various imaging techniques for MRI is not documented or readily available. The Department of Health has no information on CT or MRI for inflammatory bowel disease. HESP advises the vast majority of patients in Australia with Crohn's disease are receiving CT, while another proportion is receiving MR and a very small (next to nil) proportion would receive SBFT as CT is becoming phased out. For these estimates, the relative existing usage of imaging was therefore assumed to be 70% CT/CT enterography, 25% MR small bowel and 5% SBFT. It was further assumed that the proportion currently using MRI pelvis was 20%, 50% were using endoanal ultrasound and 30% received surgical examination. These proportions were altered in sensitivity analyses due to their high inherent uncertainty.

Further assumptions were necessary for the proportions of eligible patients that are expected to present with each of the six indications. It was assumed 100% of all new cases would require a small bowel MRI for assessing extent of disease, 20% of prevalent cases would require a small bowel MRI for complications, 0.2% with pregnancy and 20% for assessment of therapy in small bowel Crohn's disease. It was assumed 100% of patients with suspected perianal disease would require MRI pelvis and 50% would require a MRI for assessment of therapy. In the base case, the number of small bowel or pelvis MRIs per person was 1 per year for any indication. This is intended as an overall average with a small proportion of patients likely to require multiple MRIs within a 12 month period and others zero. This frequency was tested at 0.75, 1.5 and 2.0 in sensitivity analyses.

Table 25 provides the costs used in the financial estimates and their sources. The full MBS calculations are provided in Table 26. However, the estimates in the calculations were based on 85% of the proposed fees because this is what the Government normally reimburses for outpatient services. We included radiologist and surgical consultation fees with the respective procedures. Contrast was also added to MRI procedures as this is not described as being included in the proposed MBS item descriptors.

Table 25: Cost estimates used in the financial estimates

Description	Cost	Source
MRI small bowel per image	$ 627.50	Proposed by applicant and similar in complexity to MBS #63473 (staging cervical cancer)
MRI pelvis per image	$403.20	Proposed by applicant and similar in complexity to MBS #63482 (MRI for pancreas and biliary tree)
MRI enterocylsis	$265.25	Proposed by applicant (nasojejunal tube $130 + procedure $135.25) used with MRI small bowel
Contrast	$44.80	MBS item #63491
CT/CTE	$480.05	MBS item #56507
Abdominal ultrasound (for endoanal)	$55.65	MBS item #55014
Abdominal ultrasound in pregnancy	$ 60.00	MBS item #55700
SBFT	$78.95	MBS item #58915
Surgical examination (perianal)	$3,878.00	AR-DRG item #J09Z perianal procedure
Surgical consultation	$85.55	MBS item #104
Radiologist consultation	$ 85.55	MBS item #104

CD= Crohn's disease, CT = Computed Tomography, CTE = Computed Tomography enterography, MRI= magnetic resonance imaging, US= ultrasound, SBFT=small bowel follow-through

Other health resources will be used by patients being managed for Crohn's disease such as medical therapies (e.g., immunosuppression, antibiotics, biologicals, corticosteroids etc), other monitoring visits and potential hospitalisations. However, these resources were omitted from the analyses in order to focus on the imaging-related costs alone and potential cost-offsets proposed by the client. In effect, therefore, all other health costs are held constant in these financial estimates. All calculations were performed on an Excel™ spreadsheet. The results of these calculations are provided in Table 26.

Table 26: Results of the financial estimates (2014-2018) (with patient co-payment)

	2014	2015	2016	2017	2018
New cases of CD	3361	3462	3567	3675	3786
Prevalent cases of CD	47724	51186	54753	58428	62213
Total cases of Small bowel CD	23499	25138	26827	28567	30359
Total cases of Perianal CD	6130	6558	6998	7452	7920
Estimated MRI procedures by indication					
MRI small bowel - extent of CD	1546	1593	1641	1690	1741
MRI small bowel - complx of CD	4391	4709	5037	5375	5724
MRI small bowel - pregnancy	3	3	3	3	3
MRI small bowel - change in therapy	4391	4709	5037	5375	5724
MRI pelvis –extent of CD	403	415	428	441	454
MRI pelvis - change in therapy	2863	3071	3285	3506	3733
Total number of small bowel MRI tests	10330	11014	11719	12444	13192
Total number of pelvis MRI tests	3267	3487	3713	3947	4187
Total MBS costs for small bowel MRI	$7,236,726	$7,715,785	$8,209,311	$8,717,742	$9,241,528
Total MBS costs for pelvis MRI	$1,481,516	$1,581,253	$1,684,001	$1,789,853	$1,898,901
MBS cost offsets small bowel MRI[1]	$2,147,426	$2,279,532	$2,415,627	$2,555,832	$2,700,272
MBS cost offsets pelvis MRI[2]	$314,810	$336,003	$357,836	$380,329	$403,501
Reduction in surgical costs pelvis MRI	$3,800,507	$4,056,358	$4,319,937	$4,591,475	$4,871,214
Total net MBS costs	$6,256,006	$6,681,503	$7,119,849	$7,571,434	$8,036,656
Overall Net Government costs	$2,455,500	$2,625,144	$2,799,912	$2,979,958	$3,165,442

CD= Crohn's disease, complx = complications; MRI= magnetic resonance imaging

1. Reductions in consultations, CT, ultrasounds, small bowel follow through
2. Reductions in consultations and endoanal ultrasounds.

Sensitivity analyses were performed on virtually all estimates used in the model. Table 27 presents the key results for the first year and only for a selection of these analyses. The analyses presented are those with the most variation to the base results.

Table 27: Sensitivity analyses of financial estimates (selected)

Sensitivity Analyses	Net MBS costs	Net All costs
Base case	$6,256,006	$2,455,500
% small bowel - low 31%	$4,596,452	$795,945
% small bowel - high 65%	$8,358,109	$4,557,602
% of pts requiring for small bowel CD assess low 15%	$5,487,063	$1,686,556
% of pts requiring for small bowel CD assess high 25%	$7,024,950	$ 3,224,444
Lower cost of MRI small bowel (by 20%)	$5,154,028	$1,353,522
Number of tests per person per year: 0.75	$4,613,302	$812,796
Number of tests per person per year: 1.5	$9,541,415	$5,740,908
Number of tests per person per year: 2.0	$12,826,823	$9,026,316

CD= Crohn's disease, MRI = magnetic resonance imaging, pts=patients

As shown in Table 27, the financial costs are highly driven by the number of tests expected per person per year. Variation in the proportions of patients using alternative imaging tests or the proportions of patients with Crohn's disease presenting for the six indications did not materially change the base results, that is, costs varied within approximately ± $1 million. Similarly, most epidemiological indicators also did not change the results notably, with the exception of the proportion of patients with Crohn's disease with small bowel disease (Table 27).

Costs to the Medical Benefits Scheme (MBS)

The proposed fee for MRI small bowel is $627.50 based on being similar in procedural complexity to MBS item 63473 for staging cervical cancer. For MRI pelvis, the proposed fee is $403.20 based on being similar in complexity to MBS #63482 (MRI for pancreas and biliary tree). For MRI enteroclysis in small bowel, the applicant proposes the fee $265.25 which is based on the cost of a nasojejunal tube $130 + procedure $135.25. The fees proposed seem appropriate.

As shown in Table 26, the estimated net cost to the MBS for MRI for the proposed indications is $6.3 million in the first year and rising to $8.0 million by 2018. This includes cost savings for replaced MBS costs for CT, CTE, abdominal ultrasound and SBFT services.

Costs to the Australian healthcare system overall

Total costs to the Australian health system, including MBS and hospital costs, resulted in net costs of $2.5 million in the first year to $3.2 million in 2018.

Costs to the private health insurer and/or patient

Our financial estimates have assumed that 15% of the Medicare scheduled fees for MRI will be made by the patient and/or their private health insurer. In reality, what the patient pays will depend on whether the radiologist decides to bulk bill, charge the scheduled fee or charge above the scheduled fee. Currently, some private health insurers cover MRI in their products but many do not.

In MSAC application #1146.1, the average patient co-payment was $25.32 for each CT scan.

Discussion

Is it safe?

MRI small bowel and pelvis for Crohn's disease appears to be relatively safe compared with CT, SBFT, endoscopy, ultrasound and surgical examination. There were no studies reporting on the comparative safety of these alternatives however MRI is non-invasive, has clear contraindications in small number of patients and does not emit ionizing-radiation.

Table 15 provides the annual effective ionizing radiation doses from studies that have followed patients with Crohn's disease over long periods. The radiation received was largely attributable to CT radiation exposure. The effective radiation ranges were from 2.8 to 5.3 mSv (mean annually). Background exposure in Australia is 1.5 mSv per person per year. Although the exposure from CT reported in the literature is substantially higher than background levels, but still low overall, there is wide concern among health professionals that the cumulative exposure over time for a disease such as Crohn's disease, which also affects adolescents and young adults, may be harmful to health. This is supported by one study which states factors found to be associated with higher radiation exposure were children (<17 years) (hazards ratio 2.1, 95%CI: 1.1 – 4.1) and those who had multiple surgeries (hazards ratio 2.7, 95%CI: 1.4 – 5.4)(Desmond et al., 2008).

In conclusion, imaging modalities of SBFT and CT emit ionizing radiation at low levels however the combined factors of Crohn's disease requiring repeated tests, young adults and abdominal tissue, make the cumulative exposure potentially high over a lifelong disease course and may be harmful to health.

Is it effective?

The body of evidence included in this assessment was appraised using the NHMRC guidelines (NHMRC 2008). A summary of the body of evidence for the diagnostic accuracy of MRI small bowel or pelvis is presented in Table 28.

It is important to note that Table 28 does not cover all six indications proposed in this application. There were no studies identified for the subgroup of pregnant women with suspected Crohn's disease. There was poor quality evidence to assess change in management of disease following MRI for both small bowel and fistulising perianal Crohn's disease.

The evidence base was small but with two Level II accuracy studies, was considered satisfactory to address some of the research questions.

Collectively, the studies reported consistent results showing high sensitivity and high specificity. Most authors concluded that MR enterography was equivalent to CT enterography at detecting extent and complications of Crohn's disease. The factors that appear to be important in accurately detecting the many features of Crohn's disease and its manifestations are the experience of the radiologist and magnet strength (Wu et al., 2013). Although, we cannot rule out a degree of selection bias in some Level III studies

and the high level of study heterogeneity within the systematic reviews, the findings for sensitivity and specificity remained consistent.

Table 28: Completed body of evidence assessment matrix

Body of evidence (X axis) Component (Y axis)	A Excellent	B Good	C Satisfactory	D Poor
Evidence base		One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias		
Consistency		Most studies consistent and inconsistency may be explained		
Clinical impact				Unknown[1]
Generalisability			Population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	
Applicability			Probably applicable to Australian healthcare context with some caveats	

Adapted from (NHMRC, 2008a)

1. Relates to the impact of MRI small bowel and pelvis on patient outcomes

The diagnostic studies in this review did not examine any patient or clinical outcomes beyond test performance indicators. Therefore no links can be made to infer changes in management following MRI. Further research is required to determine the decisions of management in a well-designed study that improves upon the two studies assessing management patterns in this assessment (Cheriyan et al., 2013, Sanka et al., 2012). We are unable to drawn clear conclusions about these results because they were largely descriptive studies only.

Generalisability to the target population in this application is difficult to judge. This is because there were very few details provided on the study samples, for example, few studies reported the duration the patients had had Crohn's disease, concomitant medication use or prior tests or other health indicators. On the few demographics (age and gender) that were reported across the studies, these appear to be close to those in two recent Australian studies (Ng et al., 2013, Wilson et al., 2010). Hampering the generalizability across populations are the small samples involved in all studies (less than 80 patients in all studies) and the high likelihood of patient heterogeneity. However, the scarcity of Australian research in Crohn's disease may mean it is clinically sensible to apply this evidence to the target population.

The applicability of the studies to the Australian healthcare context is unclear but may be acceptable. This is due to the US and European populations studied, the developed health care systems and high experience of radiologists involved in the studies. It is unknown if the MRI machines used in the study centres within the clinical studies are the same as those in use in Australia. The studies were all published within the last ten years, with the exception of Schwartz *et al.* 2001, and therefore it adds weight to the more advanced fast-scanning MRI machines now available.

What are the economic considerations?

Due to the superior performance of MRI pelvis found in a meta-analysis comparing it to endoanal ultrasound, one cost-utility analysis was performed on one of the six proposed indications in this application. However, the analysis is simple, short-term and relies heavily on a number of assumptions relating to the clinical impact of a false negative test.

Subject to these simplifications and caveats, MRI pelvis was found to be a cost-effective strategy due to the potential for avoided surgical examination, which is relatively expensive, and may leave patients vulnerable to adverse surgical events.

The financial impact of public funding for MRI small bowel and pelvis was estimated as the potential incremental costs to the MBS and wider health care system and included all the intended uses of MRI within this application. These analyses should be interpreted cautiously given the limited epidemiological data of Crohn's disease and scarce utilisation data on the respective imaging strategies. The analyses drew on HESP advice, published evidence and two Australian epidemiological studies.

The sensitivity analyses show that the strongest factor influencing the financial estimates to the MBS and wider health system is the mean number of MRIs that would be required by the eligible patients for the proposed indications. In the base case, the mean was one MRI per person annually. If surveillance of Crohn's disease is the general intention of the MRI for small bowel and perianal disease, the number of times MRI is used will be the most important driver of costs to the MBS and wider health system. To a lesser degree, the estimated number of patients with Crohn's in the small bowel was also a notable factor. Depending on the accuracy of this proportion, the base financial estimates could vary by ±$2 million in the first year.

Conclusions

Safety

MRI appears to be a safe procedure and may be safer than CT, SBFT, endoscopy and surgical examination. This is because MRI is non-invasive, does not emit ionizing-radiation and presents no chemical or bodily harm to the patient. There are no studies to firmly establish the widely perceived comparative safety of MRI over the nominated comparators. The safety of MRI is unknown for pregnant women.

Effectiveness

Diagnostic accuracy

MR enterography appears to have equivalent sensitivity and specificity compared with CT enterography for evaluation of established Crohn's disease in the small bowel. For suspected or known fistulising perianal Crohn's disease, MRI appears to have similar sensitivity and superior specificity compared with endoanal ultrasound or surgical examination.

Impact on patient management

The poor quality of evidence precludes firm conclusions about whether patients receive earlier or more appropriately targeted surgical or medical intervention following MRI. Further research is required on this specific topic.

Impact on health outcomes

No evidence was identified to inform the direct or indirect links of MRI testing and patient health outcomes.

Economic considerations

A cost-utility analysis was performed only for MRI pelvis for detecting fistulas and abscesses in fistulising perianal Crohn's disease. The findings are exploratory and rely on some assumptions but in general suggest that MRI pelvis is cost-effective compared with endoanal ultrasound over a 12 month period.

Costing

The expected uptake of MRI small bowel and pelvis is estimated at 13597 procedures for 13597 patients annually.

The total cost to the Medical Benefits Scheme for MRI small bowel and pelvis is estimated to be $6.256 million annually.

Total cost to the Australian healthcare system including MBS for MRI small bowel and pelvis is estimated to be $2.456 million annually.

Appendix A Treatment algorithms for six proposed indications

Figure A.1: Evaluation of disease extent at time of initial diagnosis of Crohn's diagnosis

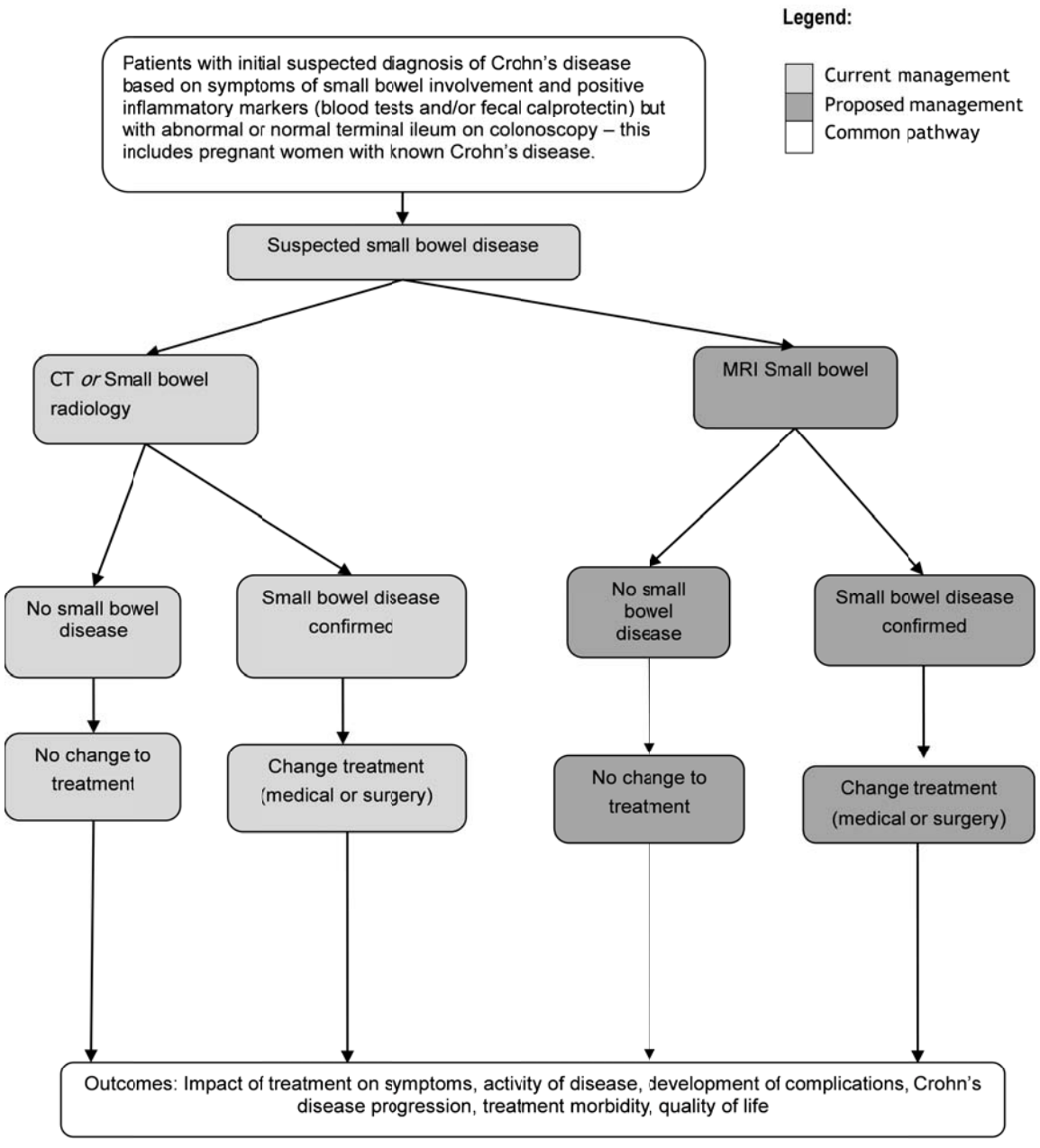


Figure A.2: Evaluation of exacerbation/suspected complications of known Crohn's disease

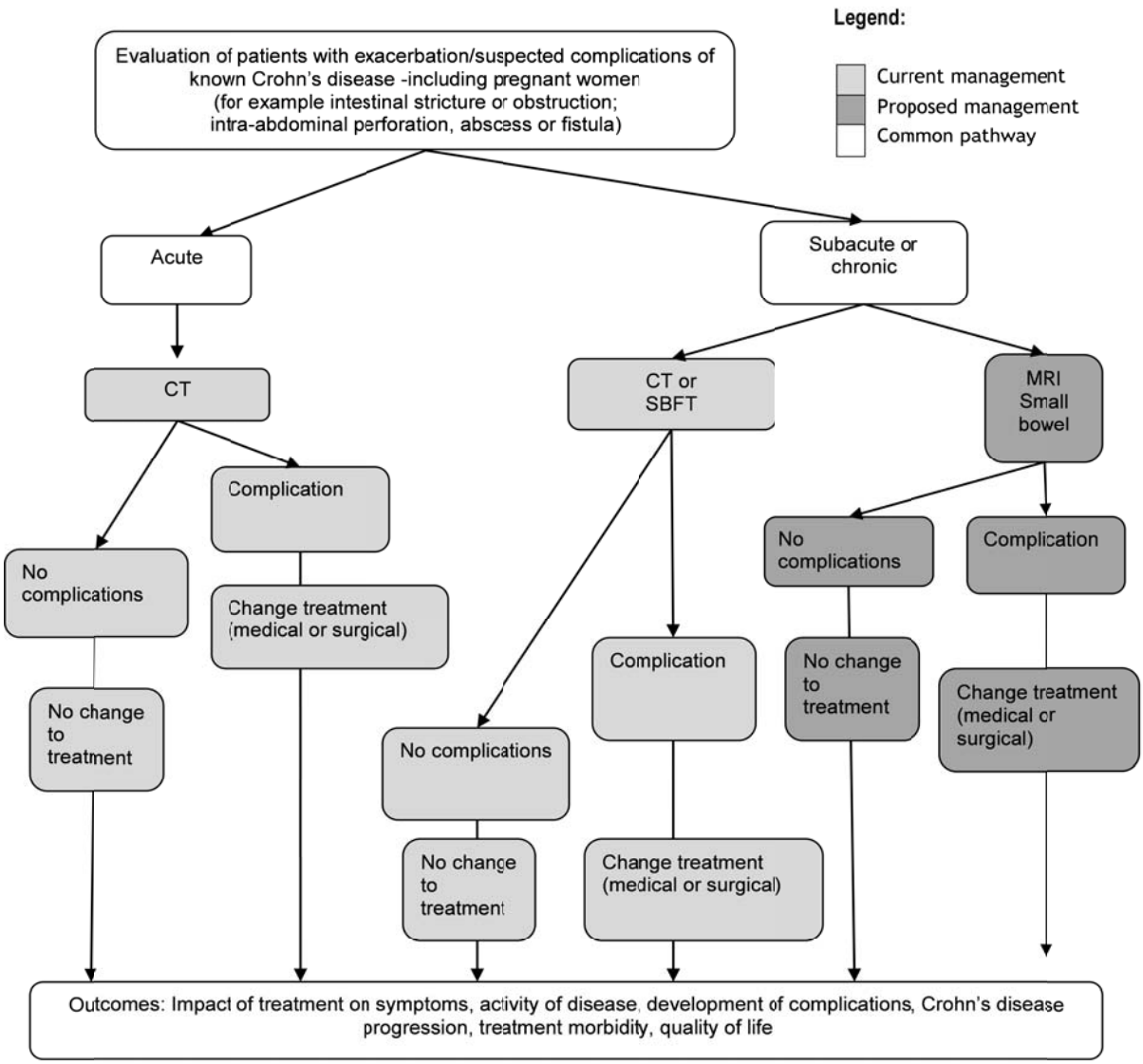


Figure A.3: Evaluation of suspected Crohn's disease in pregnancy

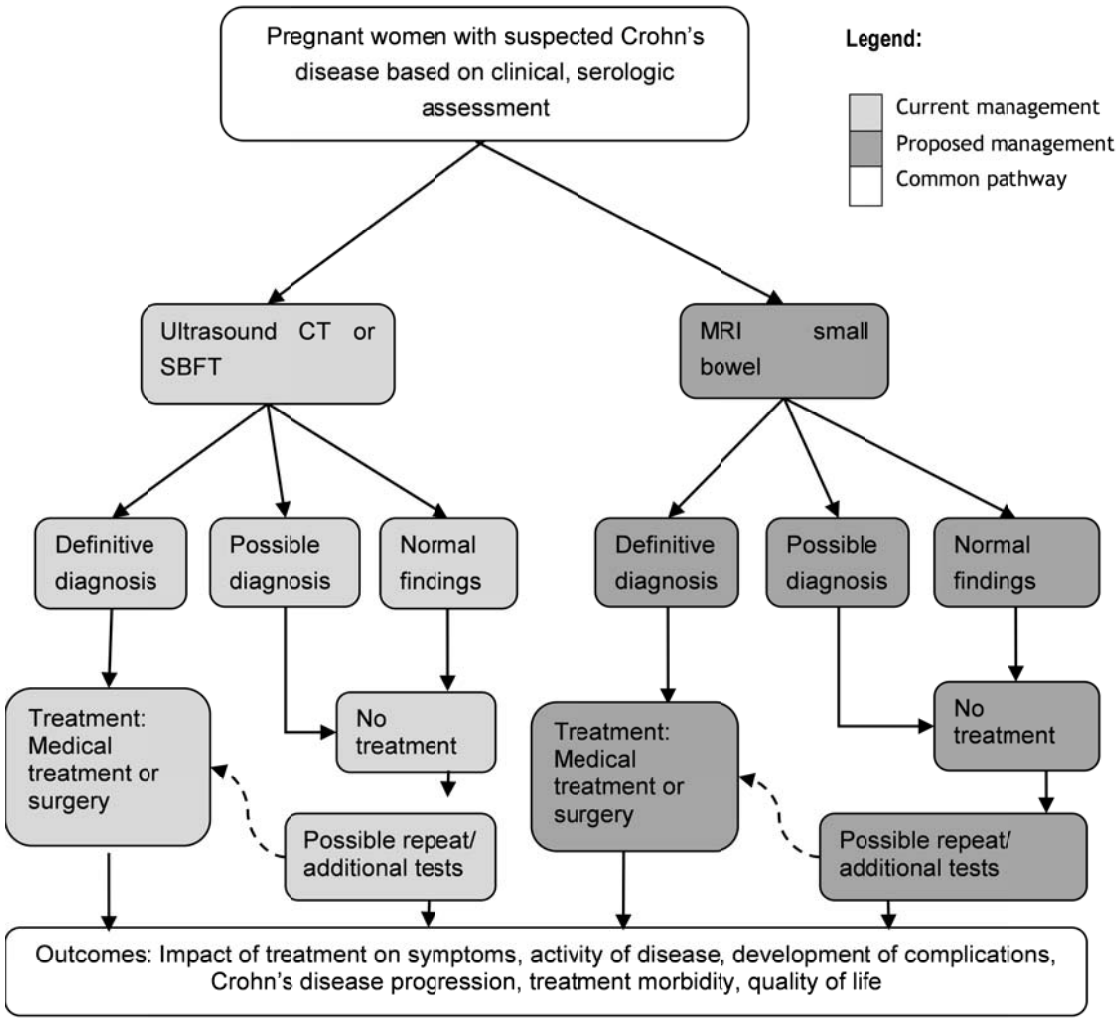


Figure A.4: Assessment of change to therapy in patients with Crohn's disease

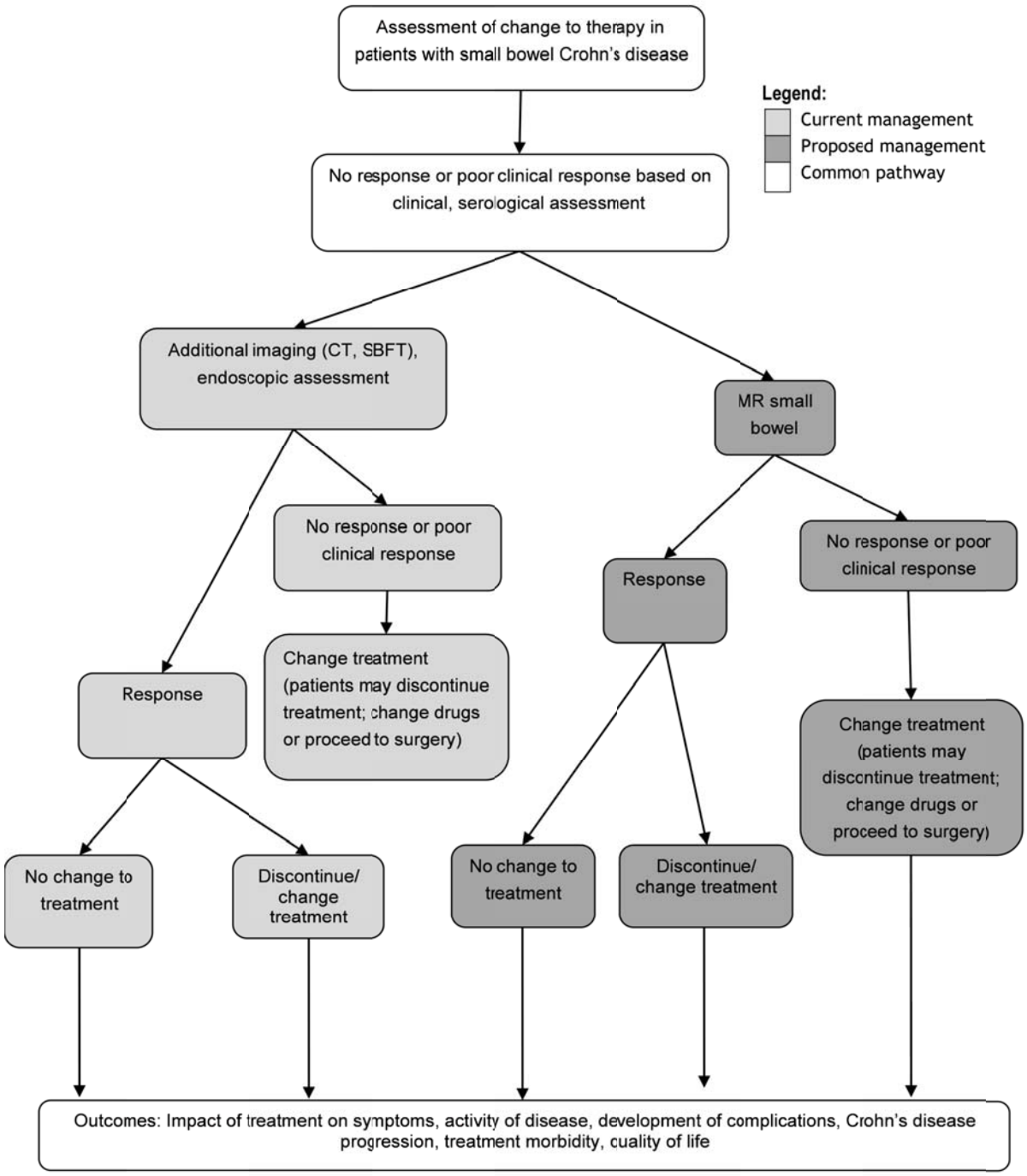


Figure A.5: Evaluation of pelvic sepsis and fistulas associated with established or suspected Crohn's disease

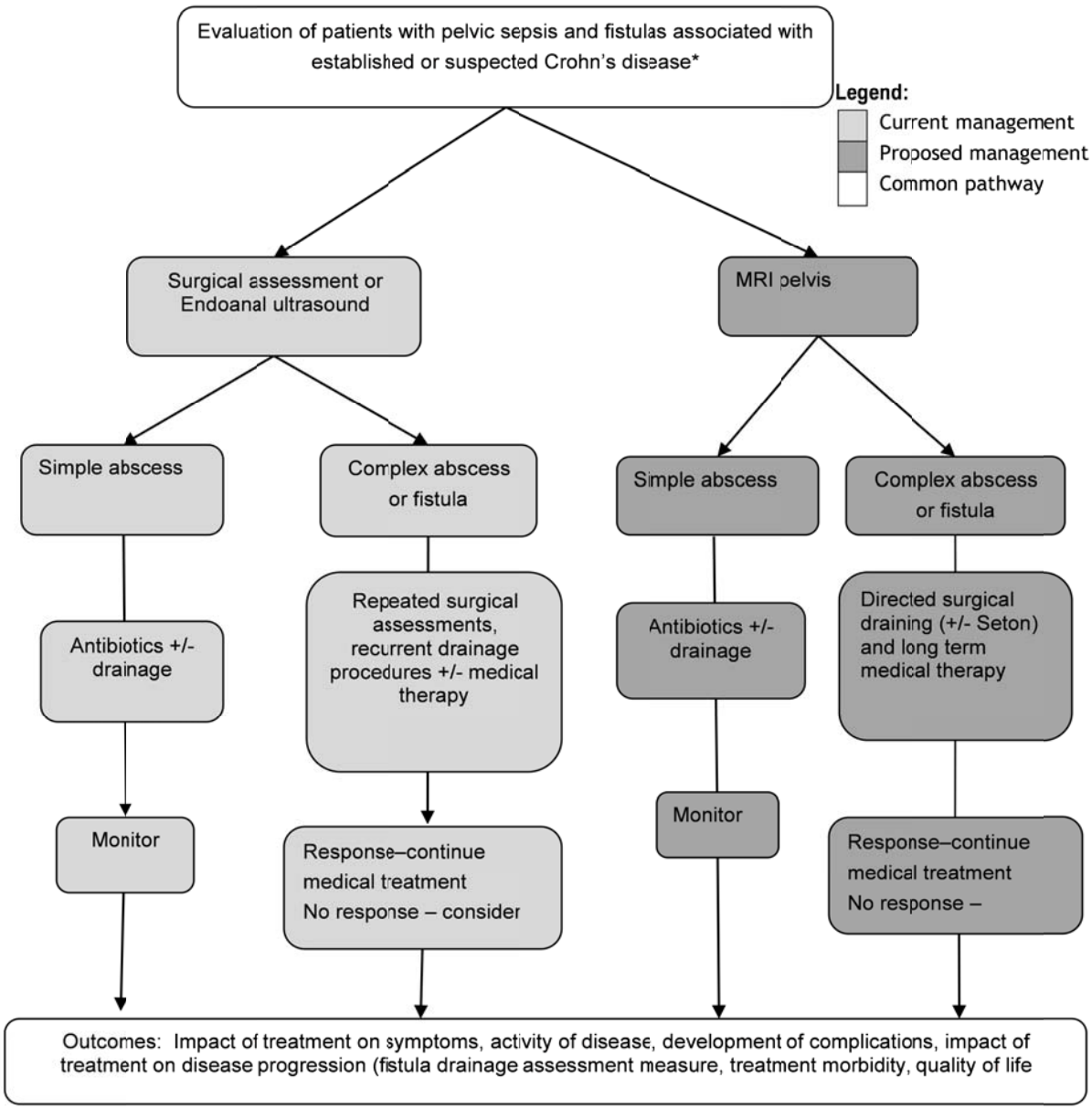
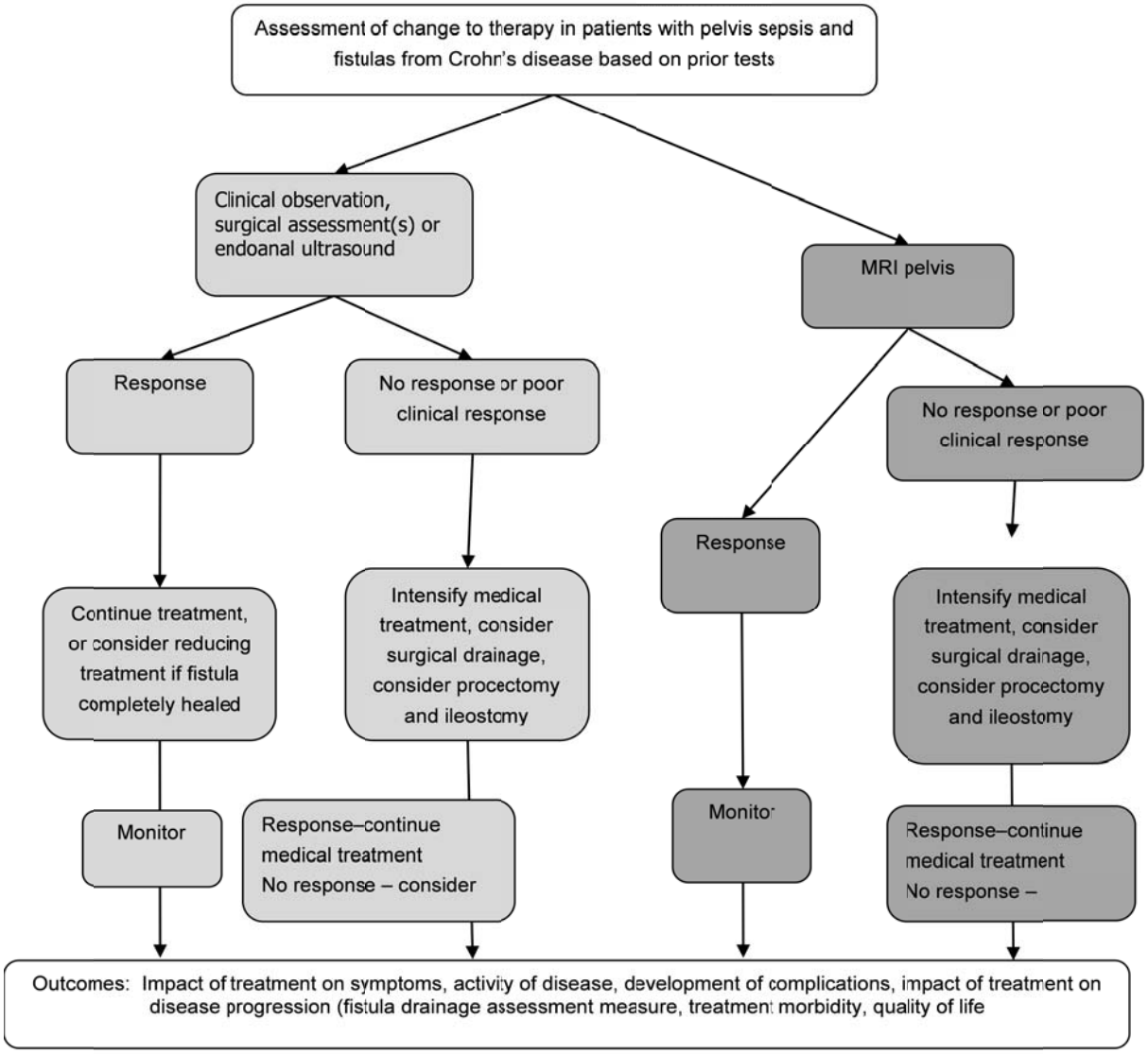


Figure A.6: Assessment of change to therapy in patients with pelvis sepsis and fistulas from Crohn's disease



Appendix B Health Expert Standing Panel Members and Evaluators

Health Expert Standing Panel Members

Member	Nomination / Expertise or Affiliation
Professor Richard Mendelson	Consultant Radiologist, Royal Perth Hospital
Associate Professor Damien Stella	Director of CT, Dept of Radiology, Royal Melbourne Hospital, University of Melbourne

Evaluators

Name	Organisation
Louisa Gordon	Griffith University
Tracy Comans	Griffith University

Appendix C Search strategies

MEDLINE Ovid MEDLINE (1946 to present with Daily Update)

Search Date: 7/11/13

No.	Search term	Results
1	Crohn*	38911
2	enteritis	12531
3	enterocolitis	13415
4	small bowel	24891
5	pelvic sepsis	331
6	fistula*	84115
7	1 or 2 or 3	62473
8	4 or 5 or 6	108080
9	7 and 8	5939
10	magnetic resonance	504038
11	MRI	131505
12	MRE	1045
13	10 or 11 or 12	524321
14	9 and 13	467
15	Limit 14 to (English language and humans and (clinical trial, all or comparative study or controlled clinical trial or evaluation studies or randomized controlled trial or systematic reviews)	114
16	fistulising	80
17	7 and 16	68
18	perianal	4647
19	18 and 17	12
20	Limit 19 to (English language and humans and (clinical trial, all or comparative study or controlled clinical trial or evaluation studies or randomized controlled trial or systematic reviews)	1

115 citations exported into Word files for further filtering. Titles & abstracts read for relevance (1st screen).

Excluded: 73	Results
Duplicates	5
Included in systematic reviews	4
Wrong or no comparator	29
Wrong disease	6
Wrong intervention	20
Wrong purpose	2
Wrong study type	7

42 articles downloaded for relevance (PDFs retrieved)

Excluded: 30	Results
Less than 20 patients with CD	3
All IBD, CD not differentiated	2
Included in systematic reviews	3
Wrong comparator	11
Wrong intervention	2
Wrong purpose or outcome	5
Wrong study type	1
Insufficient outcome data	2
Study superseded by later study	1

Final numbers: 12 studies - 3 systematic reviews, 9 clinical studies.

The Cochrane Library

Search Date: 15/11/13

No.	Search term	Results
1	Crohn* ti: ab,kw in Cochrane Reviews (Reviews only), Trials, Technology Assessments and Economic Evaluations	1221
2	enteritis	313
3	enterocolitis	832
4	small bowel	2057
5	pelvic sepsis	156
6	fistula*	1527
7	1 or 2 or 3	2317
8	4 or 5 or 6	3513
9	7 and 8	5558
10	magnetic resonance	7595
11	MRI	3753
12	MRE	18
13	10 or 11 or 12	8461
14	9 and 13 in Cochrane Reviews (Reviews only), Trials, Technology Assessments and Economic Evaluations	147
15	14 and 1	19
16	fistulising	10
17	7 and 16	4
18	perianal	282
19	18 and 17	1

21 retrieved for filtering, 9 duplicates (from MEDLINE search), 12 new hits

Excluded: 9	
Wrong comparator	3
Wrong intervention	6
Included: 3	

3 for further full text filtering – all included

Grand 2012, Cipriano 2012 ec econ, Levesque 2012 ec econ

Clinical trials registers:

	# hits	Relevant
Current Controlled Trials www.controlled-trials.com	85	0
ControlledTrials.gov www.clinicaltrials.gov	13	1 (duplicate)
Australian New Zealand Clinical Trials Registry www.anzctr.org.au	0	0
WHO International Clinical Trials Registry Platform http://apps.who.int/trialsearch	6	0

HTA Agencies:

	#hits	Relevant
Centres for Reviews and Dissemination http://www.york.ac.uk/CRDweb	0	0
International Network of Agencies for Health Technology Assessment (INAHTA) http://www.inahta.org/	6	0

Appendix D Studies included in the review

Study profiles of included systematic reviews

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Test comparison	Conclusions/recommendation	Quality assessment
Wu et al (2013)	To evaluate the overall diagnostic accuracy of MRI is assessing the activity of CD in the small bowel.	17 studies (n=725 patients) Search methods: Publications from Jan 2001 to Sept 2011 were selected from MEDLINE, EMBASE and other electronic databases. Studies were included if MRI was used to assess active CD in the small bowel, 9/14 QUADAS criteria were fulfilled for methodological quality, sufficient raw data were reported, studies applied histopathologic and ileocolonoscopy assessment as referent standard, >10 patients.	Mean age range 8 to 77 years Patients in which MR can be used to evaluate active CD. Test: MR Comparator: None Referent: Ileocolonoscopy and histopathologic assessment.	MRI has high sensitivity and specificity for diagnosis of active CD in the small bowel and is a suitable modality for imaging and surveillance of active CD.	HIGH QUALITY Was the research question specified? Yes Was the search strategy explicit and comprehensive? Yes Were the eligibility criteria explicit and appropriate? Yes Was a quality assessment of included studies undertaken? Yes Were the methods of the study appraisal reproducible? Yes Were sources of heterogeneity explored? Yes Was a summary of the main results clear and appropriate? Yes
Meta-analysis pooled results: Sensitivity 0.87 (95%CI: 0.77, 0.93) I2 = 0.98 (strong evidence of significant heterogeneity) Specificity 0.91 (95%CI: 0.81, 0.96) Overall AUC(ROC) 0.95 (95%CI: 0.93, 0.97) Authors conclusions: Results showed MRI had good diagnostic accuracy and good clinical utility Using meta-regression analyses, magnet strength and experience of the radiologist were the most important variables influencing sensitivity. Common weaknesses in the included studies were whether interpretation of pathology was blinded from MRI. Funnel plot asymmetry tests showed no major publication bias.					

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Test comparison	Conclusions/recommendation	Quality assessment
Siddiqui et al (2012)	To undertake a systematic review to compare endoanal ultrasound or MRI for perianal fistulas in Crohn's disease.	4 studies (n=113 patients) Search methods: Publications from Jan 1970 to Oct 2010 were selected from MEDLINE, EMBASE and other electronic databases. Studies were included if they compared MRI with endoanal ultrasound for patients with suspected perianal fistulas. Excluded if the surgical standard was not applied.	Mean age range 17 to 76 years Test: MR Comparator: Endoanal ultrasound Referent: Examination under anaesthetic	MRI has similar sensitivity to endoanal ultrasound but may have better specificity for identifying the presence of perianal fistulas in CD. Small number of studies and high heterogeneity between studies precludes any firm conclusions.	HIGH QUALITY Was the research question specified? Yes Was the search strategy explicit and comprehensive? Yes Were the eligibility criteria explicit and appropriate? Yes Was a quality assessment of included studies undertaken? Yes (QUADAS used and reported) Were the methods of the study appraisal reproducible? Yes Were sources of heterogeneity explored? Yes Was a summary of the main results clear and appropriate? Yes
Meta-analysis pooled results for fistula detection: MRI Sensitivity 0.87 (95%CI: 0.63, 0.96) I2 = 0.93 (strong evidence of significant heterogeneity) Specificity 0.69 (95%CI: 0.51, 0.82) Endoanal ultrasound Sensitivity 0.87 (95%CI: 0.70, 0.95) I2 = 0.92 (strong evidence of significant heterogeneity) Specificity 0.43 (95%CI: 0.21, 0.69) Authors conclusions: Results showed MRI had comparable sensitivity and possibly better specificity for identifying fistulas. Findings are important because when clinicians can understand the fistula, it can assist with sphincter preservation and adequate treatment. Common weaknesses in the included studies were whether blinding occurred at the time of endoanal ultrasound and the different use of standard tests (most were examination under anaesthetic) but one included the index test into the overall outcomes (incorporation bias). Some time delay may be problematic in some studies. Overall quality of QUADAS assessments were 'good'.					

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Test comparison	Conclusions/recommendation	Quality assessment
Panes et al (2011)	To undertake a systematic review to compare ultrasound, CT and MRI for diagnosis, assessment of activity and complications of Crohn's disease.	68 studies Search methods: Publications from Jan 1994 to Dec 2010 were selected from MEDLINE, EMBASE. Studies were included if they compared MR ± ultrasound ± CT, had an adequate reference standard, prospective design, data allowed for calculation of sensitivity / specificity etc. No additional formal quality assessment was performed.	Mean age range – not clear Test: MR, CT, ultrasound Comparator: Not clear (Few studies included direct comparisons of imaging tests, most were single test with a referent) Referent: Either ileocolonoscopy, capsule endoscopy, enteroscopy, surgery, pathology.	Cross sectional imaging techniques have high accuracy for evaluation of CD, reliably measure complications and disease severity. Lack of established reference standard and small sample sizes in the included studies precludes any firm conclusions. Many studies use different definitions of disease parameters.	LOW QUALITY Was the research question specified? Yes Was the search strategy explicit and comprehensive? Yes Were the eligibility criteria explicit and appropriate? Yes Was a quality assessment of included studies undertaken? No Were the methods of the study appraisal reproducible? Unclear Were sources of heterogeneity explored? N/A Was a summary of the main results clear and appropriate? No
Direct comparison of different imaging techniques for assessment of location and extent of inflammatory lesions in CD (one relevant study Fiorino et al. 2011) MRI: Sensitivity 0.88 Specificity 0.88 CT: Sensitivity 0.88 Specificity 0.88 Direct comparison of different imaging techniques for detection of activity in CD (4 relevant studies: Fiorino 2011, Lee 2009, Siddiki 2009, Low 2000) (Ranges presented – unpooled) MRI: Sensitivity 0.80-0.91 Specificity 0.67-1.00 CT: Sensitivity 0.60-0.95 Specificity 0.80-1.00 Direct comparison of different imaging techniques for assessment of severity in CD (1 relevant study: Pascu 2004) MRI no luminal contrast vs ultrasound: ultrasound showed better correlation with endoscopic findings (r>0.80) than MRI (r>0.50) Direct comparison of different imaging techniques for assessment of stenosis in CD (1 relevant study Fiorino et al. 2011) MRI: Sensitivity 0.92 Specificity 0.90 CT: Sensitivity 0.85 Specificity 1.00 Direct comparison of different imaging techniques for assessment of fistulas and abscesses in CD (1 relevant study Lee et al. 2011) MRI: Sensitivity 1.00 Specificity 1.00 CT: Sensitivity 1.00 Specificity 1.00					

Study profiles of included clinical studies on diagnostic accuracy and change in management

Author/Year/Country Setting/ N	Study objective and design	Study population	Results	Quality assessment
Cheriyan et al (2012) Ireland, single centre N=57	Objective: To determine whether MR enterography influenced the medical an surgical management of patients with small bowel CD Study design: Retrospective, consecutive Timing: 01/2007-12/2010 Index test: MR enterography Comparator test: n/a Timing interval: n/a Reference test: n/a Test interpretation: MR enterography evaluated by one radiologist with expertise in gastrointestinal imaging.	Inclusion/exclusion criteria Inclusion: histologically confirmed CD, underwent MR enterography for symptom and disease assessment Exclusion: Management options not clearly stated after MR enterography, or occurred after 1 month of MR enterography Patient characteristics: Age/Gender: 47% male, median age 36 years (range 16-68), prior surgery 39 (68%) Length of time with Crohn's disease: 9.5 years (range 1 – 35) Prior tests: Not stated Clinical characteristics: Symptoms not stated 68% had previous surgery	Change in management 7 patients had normal MR enterography 50 patients had abnormal MR enterography (5 stricturing, 17 active, 14 both active and structuring) 6/7 patients with normal MR enterography had no change in management 42 patients had a change in management, 22 (53%) had medical intervention and 20 (47%) underwent surgery. Conclusion: High clinical impact on patient management. Patients with abnormal imaging had significantly more changes in management both surgical and medical.	NHMRC level of evidence: IV Quality: Q3 POOR Comparison: C1: other comparison (no comparison) Applicability: P2 limited (unclear) QUADAS Prospective: no Consecutive: unclear/yes Explicit selection criteria: yes Reference standard: n/a Test interval in days/weeks: n/a Tests and ref std well described/reproducible: yes Tests assessed and independent of ref std: n/a Ref std assessed and blinded to other tests: n/a Routine clinical data available: yes Uninterpretable/intermed results reported: no Study withdrawals explained: n/a Sufficient data for 2x2 table: n/a Relevant population: yes Applicable comparator: n/a Applicable intervention: yes

Author/Year/Country Setting/ N	Study objective and design	Study population	Results	Quality assessment
Sanka et al (2012) England, single centre N=34	Objective: To report on the outcomes of performing magnetic resonance enteroclysis in the diagnosis and management of children with inflammatory bowel disease. Study design: Retrospective Timing: 09/2008-11/2010 Index test: MR enteroclysis. Previous afternoon upper endoscopy to place naso-jejunal tube. Comparator test: n/a Timing interval: n/a Reference test: n/a Test interpretation: MR enteroclysis evaluated by one radiologist with expertise in gastrointestinal imaging.	Inclusion/exclusion criteria Inclusion: confirmed or suspected CD or ulcerative colitis Exclusion: not stated Patient characteristics: Age/Gender: 45% male, mean age 15.3 years, CD confirmed in 19 patients Length of time with Crohn's disease: not stated Prior tests: Not stated Clinical characteristics: Symptoms not stated	Confirming a diagnosis 8 normal MRE – patients discharged 1 normal MRE – no changes Changes in management 2 patients commenced azathioprine 7 patients commenced infliximab, 4 had ileo-caecal resection, adalimumab in 3 patients, 1 patient referred to psychological support, 6 patients for complx, 5 normal and continued current management, 1 significant complx, Other – one underwent surgery, one patient commenced methotrexate Limitations in use of MR enterocylsis 2 patients did not complete MR enterogclysis (1 extreme discomfort from stricture, 1 claustrophobia)	NHMRC level of evidence: IV Quality: Q3 POOR Comparison: C1: other comparison (no comparison) Applicability: P2 limited (unclear) QUADAS Prospective: no Consecutive: unclear/yes Explicit selection criteria: yes Reference standard: n/a Test interval in days/weeks: n/a Tests and ref std well described/reproducible: yes Tests assessed and independent of ref std: n/a Ref std assessed and blinded to other tests: n/a Routine clinical data available: yes Uninterpretable/intermed results reported: no Study withdrawals explained: yes Sufficient data for 2x2 table: n/a Relevant population: yes Applicable comparator: n/a Applicable intervention: yes

Author/Year/Country Setting/ N	Study objective and design	Study population	Results	Quality assessment
Malgras et al (2012) France, single centre N=52	Objective: To determine and compare the diagnostic accuracy of MR enterography and CT enterocylsis for detecting extent of disease and predicting operative approach. Study design: Retrospective Timing: 01/2006 - 11/2010 Index test: MR enterography Comparator test: CT enteroclysis (Patients received either the index or comparator test) Timing interval: immediately after each other in alternating order Reference test: surgical exam and pathology Test interpretation: One radiologist and one abdominal surgeon in consensus. Separate assessment of reference standard blinded to index and comparator tests.	Inclusion/exclusion criteria Inclusion: patients with established CD recommended for surgery Exclusion: Imaging tests undergone within 3 months of operation, not presented with CD (e.g. peritonitis, gastrointestinal bleeding). Patient characteristics: Age/Gender: 56% male, mean age 37, range 18-69 years. Length of time with Crohn's disease: Mean duration of medical treatment for CD 9.5 years Prior tests: videocolonoscopy Clinical characteristics: 33% patients already had surgery for CD All patients received medications for CD.	Test Accuracy Lesions present MR - Sensitivity 1.00 (95%CI: 0.92, 1.00) CT - Sensitivity 0.93 (95%CI: 0.82, 0.99) No significant difference between sensitivity between two imaging tests (p=0.242). Joint sensitivity of imaging for stenosis, abscesses and fistulas reported only. Impact on operative approach Imaging allowed correct estimation of disease in 49/52 patients 94% (95%CI: 84%-99%). Discrepancy in 3/52 patients in pre-op imaging and actual operative approach. Open laparotomy 34 (65%) and laparoscopic approach in 18 (35%)	NHMRC level of evidence: IV Quality: Q3 POOR Comparison: CX: other comparison Applicability: P1 applicable QUADAS Prospective: no Consecutive: unclear Explicit selection criteria: no Reference standard: surgical exam and pathology • Valid: yes • Applied to all patients: Yes Test interval in days/weeks: • Comparator: n/a patients received either index or comparator test • Ref std: not stated Tests and ref std well described/reproducible: yes Tests assessed and independent of ref std: yes Ref std assessed and blinded to other tests: no Routine clinical data available: yes Uninterpretable/intermed results reported: unclear Study withdrawals explained: n/a Sufficient data for 2x2 table: no Relevant population: yes Applicable comparator: yes Applicable intervention: yes

Author/Year/Country Setting/ N	Study objective and design	Study population	Results	Quality assessment
Jensen et al (2011) Denmark, multicentre N=50	**Objective:** To determine and compare the diagnostic accuracy of MR enterography and CT enterography for detection of small bowel lesions with emphasis on stenoses **Study design:** Prospective **Timing:** 10/2007-08/2009 **Index test:** MR enterography **Comparator test:** CT enterography **Timing interval:** immediately after each other in alternating order **Reference test:** surgical exam ± enteroscopy or ileoscopy **Test interpretation:** Endoscopists blinded to results of MR enterography and CT enterography. Separate radiologists (>10 yrs experience) were randomly assigned to assess MR enterography or CT enterography,blinded to other imaging.	**Inclusion/exclusion criteria** Inclusion: >=15 years, established CD based upon endoscopic, histological, radiological and surgical findings, symptomatic patients requiring assessment to change treatment strategy Exclusion: acute bowel obstruction, elevated serum-creatinine, severe claustrophobia, cardiac pacemaker, implanted magnetic foreign bodies, pregnancy, lactation. **Patient characteristics:** **Age/Gender:** 26% male, median age 39 **Length of time with Crohn's disease:** Median 10 years **Prior tests:** As above **Clinical characteristics:** Abdominal pain n=48 Diarrhea n= 32 Weight loss >3 kg n=14 Fever n=3	**Test Accuracy** <u>Detection of disease activity:</u> MR enterography Sensitivity: 74% (CI: 57%-88%) Specificity: 80% (CI: 44%-98%) PPV: 93% (CI: 77%-99%) NPV: 47% (CI: 23%-72%) CT enterography Sensitivity: 83% (CI: 66%-93%) Specificity: 70% (CI: 35%-93%) PPV: 91% (CI: 75%-98%) NPV: 54% (CI: 25%-81%) Prevalence of CD: 78% <u>Detection of small bowel stenosis:</u> MR enterography Sensitivity: 55% (CI: 32%-77%) Specificity: 92% (CI: 74%-99%) PPV: 85% (CI: 55%-98%) NPV: 72% (CI: 53%-86%) CT enterography Sensitivity: 70% (CI: 46%-88%) Specificity: 92% (CI: 74%-99%) PPV: 88% (CI: 62%-98%) NPV: 79% (CI: 60%-92%) Prevalence of stenosis: 44%	NHMRC level of evidence: II **Quality:** Q1 HIGH **Comparison:** C1: direct comparison **Applicability:** P1 applicable QUADAS Prospective: yes Consecutive: unclear Explicit selection criteria: yes Reference standard: surgical exam or ileoscopy • Valid: yes • Applied to all patients: No (5 did not receive it) Test interval in days/weeks: • Comparator: 51 minutes (range 34-91) • Ref std: surgical exam or ileoscopy performed mean 51 days (range 3-211) Tests and ref std well described/reproducible: yes Tests assessed and independent of ref std: yes Ref std assessed and blinded to other tests: yes Routine clinical data available: yes Uninterpretable/intermed results reported: no Study withdrawals explained: yes (2 because interval between tests were too long ,75-84 days) Sufficient data for 2x2 table: yes **Relevant population:** yes **Applicable comparator:** yes **Applicable intervention:** yes

Author/Year/Country Setting/ N	Study objective and design	Study population	Results	Quality assessment
Ippolito et al (2010) Italy, single centre N=29	Objective: To assess the agreement between MR enterography and CT enterography in assessing extent of small bowel CD in patients Study design: Prospective Timing: Not stated Index test: MR enterography Comparator test: CT enterography Timing interval: immediately after each other Reference test: none Test interpretation: 1 radiologist all with >10 yrs experience.	Inclusion/exclusion criteria Inclusion: known CD biopsy proven with clinical suspicion of relapse, CD Activity Index > 150, and at least one elevated acute phase reactant (erythrocyte sedimentation rate or C-reactive protein active > 5 mg/dL). Exclusion: contraindications for MRI (electrically, magnetically, or mechanically activated devices; central nervous system hemostasia clips, or the inability to administer a gadolinium contrast agent because of known allergic problems), pregnancy, renal insufficiency, and documented adverse reaction to iodinated contrast material Patient characteristics: Age/Gender: 69% male, CD confirmed, age 14-70 years Length of time with Crohn's disease: Median 10 years Prior tests: Not stated. Clinical characteristics: Not stated	Test Agreement study (no referent) <u>Detection of disease activity:</u> 100% agreement 19 MR enterography and CT enterography positive, 100% agreement 10 MR enterography and CT enterography negative Cohen's kappa =1.0 <u>Detection of fistulas</u> MR enterography and CT enterography both positive=2, MR enterography positive, CT enterography negative = 3 MR enterography negative, CT enterography positive = 0 MR enterography and CT enterography both negative = 24 Cohens kappa = 0.52 (CI 0.08-0.97) No patient was found to have abscesses. MR enterography and CT enterography have a similar accuracy in the identification of active CD in small bowel. These findings show MR enterography is more accurate in detection of enteric fistulas and sinus tracts than CT enterography.	NHMRC level of evidence: IV Quality: Q3 POOR Comparison: C1: direct comparison Applicability: P1 applicable QUADAS n/a Prospective: yes Consecutive: yes Explicit selection criteria: yes Reference standard: no Test interval in days/weeks: not stated Tests and ref std well described/reproducible: yes Tests assessed and independent of ref std: n/a Ref std assessed and blinded to other tests: n/a Routine clinical data available: yes Uninterpretable/intermed results reported: no Study withdrawals explained: yes (2 because interval between tests were too long ,75-84 days) Sufficient data for 2x2 table: no (no referent) Relevant population: yes Applicable comparator: yes Applicable intervention: yes

Author/Year/Country Setting/ N	Study objective and design	Study population	Results	Quality assessment
Schmidt et al (2010) Switzerland, single centre N=57	Objective: To assess the agreement between MR enterography and CT enterography in assessing extent of small bowel CD in patients Study design: Prospective Timing: Not stated Index test: MR enterography Comparator test: CT enterography Timing interval: < 24 hours Reference test: Composite of surgery, endoscopy and long-term follow-up Test interpretation: 3 radiologists, independent and blind assessments	Inclusion/exclusion criteria Inclusion: histologically proven CD, emergency presentation for acute exacerbation Exclusion: contraindications for MRI acute or chronic renal failure, lack of proof of CD Patient characteristics: Age/Gender: 69% male, CD confirmed, mean age 33.5 range (17-69 years) Length of time with Crohn's disease: Median 10 years Prior tests: Not stated. Clinical characteristics: Not stated	Test Accuracy <u>Bowel wall thickening</u> MR enterography Sensitivity: 84% Specificity: 91% CT enterography Sensitivity: 93% Specificity: 67% <u>Fistula</u> MR enterography Sensitivity: 86% Specificity: 93% CT enterography Sensitivity: 89% Specificity: 98% <u>Abscess</u> MR enterography Sensitivity: 79% Specificity: 99% CT enterography Sensitivity: 83% Specificity: 97%	NHMRC level of evidence: IV Quality: Q2 MEDIUM Comparison: CX: other comparison Applicability: P1 applicable QUADAS Prospective: yes Consecutive: yes Explicit selection criteria: yes Reference standard: composite • Valid: yes • Applied to all patients: yes Test interval in days/weeks: • Comparator: same day • Ref std: not stated Tests and ref std well described/reproducible: yes Tests assessed and independent of ref std: no Ref std assessed and blinded to other tests: no Routine clinical data available: yes Uninterpretable/intermed results reported: no Study withdrawals explained: none Sufficient data for 2x2 table: yes Relevant population: yes Applicable comparator: yes Applicable intervention: yes

Author/Year/Country Setting/ N	Study objective and design	Study population	Results	Quality assessment
Schreyer et al (2010) Germany, single centre N=53	Objective: To assess the diagnostic value CT (contrast-enhanced) and MR enterography in evaluation of small bowel Crohn's disease in an emergency setting. Study design: Retrospective, consecutive Timing: 01/2006 – 05/2008 Index test: Multi-detector CT(contrast orally and rectally and intravenously) Comparator test: MRI enterography Timing interval: CT and MR within 2 days. CT performed first in all patients. Reference test: none Test interpretation: 2 radiologists with 3 and 7 years experience, consensus reading	Inclusion/exclusion criteria Inclusion: known CD, patients presenting to the emergency department with acute abdominal pain Exclusion: Not stated Patient characteristics: Age/Gender: 57% Male, age range 18-73 years, median 37 years, most patients were ill with advanced CD Length of time with Crohn's disease: Not stated Prior tests: Not stated. Clinical characteristics: Not stated	Test Agreement study (no referent) MRI <u>Detection of disease activity:</u> Jejunum 32/53 (60%) Ileum 47/53 (89%) Terminal Ileum 49/53 (92%) <u>Detection of complications</u> Fistulas 27/53 (51%) Abscess 32/53 (60%) Enlarged lymph nodes >1cm 37/53 (70%) CT <u>Detection of disease activity:</u> Jejunum 32/53 (60%) Ileum 46/53 (87%) Terminal Ileum 49/53 (92%) <u>Detection of complications</u> Fistulas 25/53 (47%) Abscess 32/53 (60%) Enlarged lymph nodes >1cm 49/53 (92%) CT significantly superior to MRI for detecting enlarged lymph nodes ($p<0.001$). Conclusion: Patients with advanced CD presenting with acute abdominal pain may be sufficiently assessed with CT.	NHMRC level of evidence: IV Quality: Q3 POOR Comparison: C1: direct comparison Applicability: P2 limited QUADAS n/a Prospective: no Consecutive: yes Explicit selection criteria: no Reference standard: n/a Test interval in days/weeks: 2 days Tests and ref std well described/reproducible: yes Tests assessed and independent of ref std: n/a Ref std assessed and blinded to other tests: n/a Routine clinical data available: not stated Uninterpretable/intermed results reported: no Study withdrawals explained: not stated Sufficient data for 2x2 table: no Overall Ranking: n/a Relevant population: yes Applicable comparator: yes Applicable intervention: yes

Author/Year/Country Setting/ N	Study objective and design	Study population	Results	Quality assessment
Schwartz et al (2001) USA, single centre N= 34	Objective: To determine accuracy of endoscopic ultrasound and MRI in detection of perianal fistulas in CD Study design: Prospective, diagnostic accuracy study Timing: 07/1999-09/2000 Index test: pelvic MR Comparator tests: endoscopic ultrasound, surgical examination under anaesthesia Timing interval: not stated Reference test: Consensus of combined three tests above. Test interpretation: Triple blind comparisons, 3 physicians. 85% accuracy with consensus reference was considered clinically useful	Inclusion/exclusion criteria Inclusion: Patients with CD and suspected perianal fistulas. Exclusion: Pregnancy, contraindicated to pelvic MRI (implanted metal devices), those in need of immediate abdominal surgery for active gastrointestinal bleeding, obstruction, or intra-abdominal abscess, severe anal stenosis that precluded endoscopy. Patient characteristics: Age/Gender: 50% male, mean age 36 (age range 18-70 years) Length of time with Crohn's disease: Not stated. Prior tests: No other preoperative imaging Clinical characteristics: 65% immunosuppressive therapy, 41% infliximab or antiTNF, 56% antibiotics 18 (53%) patients had undergone previous surgery for perianal disease	Test Accuracy N=32 available for analysis 2 withdrew: 1 claustrophobia, 1 immediate surgery Rectal endoscopic ultrasound correct in 29/32 91% (CI 75%-98%) Pelvic MRI correct in 26/30 87% (CI 69%-96%) Surgical exam correct in 29/32 91% (CI 75%-98%)	NHMRC level of evidence: II Quality: Q3 POOR Comparison: CI: direct comparison Applicability: P1 applicable QUADAS Prospective: yes Consecutive: unclear Explicit selection criteria: yes Reference standard: endoscopy • Valid: no (includes index test) • Applied to all patients: yes Test interval in days/weeks: • Comparator: not stated • Ref std: not stated Tests and ref std well described/reproducible: yes Tests assessed and independent of ref std: yes Ref std assessed and blinded to other tests: yes Routine clinical data available: no Uninterpretable/intermed results reported: no Study withdrawals explained: yes Sufficient data for 2x2 table: yes Relevant population: yes Applicable comparator: no Applicable intervention: yes

Appendix E Excluded studies

Incorrect comparator

Sinha R, Murphy P, et al. Diagnostic accuracy of high-resolution MR enterography in Crohn's disease: Comparison with surgical and pathological specimen. *Clinical Radiology*. 2013;68:917-27.

Neubauer H, Pabst T, et al. Small-bowel MRI in children and young adults with Crohn disease: retrospective head-to-head comparison of contrast-enhanced and diffusion-weighted MRI. *Pediatr Radiol*. 2013;43:103-14.

Wiarda BM, Mensink PB, et al. Small bowel Crohn's disease: MR enteroclysis and capsule endoscopy compared to balloon-assisted enteroscopy. *Abdom Imaging*. 2012;37:397-403.

Sauer CG, Middleton JP, et al. Comparison of magnetic resonance enterography with endoscopy, histopathology, and laboratory evaluation in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr*. 2012;55:178-84.

Zappa M, Stefanescu C, et al. Which magnetic resonance imaging findings accurately evaluate inflammation in small bowel Crohn's disease? A retrospective comparison with surgical pathologic analysis. *Inflamm Bowel Dis*. 2011;17:984-93.

Jensen MD, Nathan T, et al. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CT enterography. *Clin Gastroenterol Hepatol*. 2011;9:124-9.

Horsthuis K, Ziech ML, et al. Evaluation of an MRI-based score of disease activity in perianal fistulizing Crohn's disease. *Clin Imaging*. 2011;35:360-5.

Gmerek L, Katulska K, et al. Usefulness of magnetic resonance enterography in diagnosis of Crohn's disease. *Pol Przegl Chir*. 2011;83:244-9.

Bocker U, Dinter D, et al. Comparison of magnetic resonance imaging and video capsule enteroscopy in diagnosing small-bowel pathology: localization-dependent diagnostic yield. *Scand J Gastroenterol*. 2010;45:490-500.

Sharman A, Zealley IA, et al. MRI of small bowel Crohn's disease: determining the reproducibility of bowel wall gadolinium enhancement measurements. *Eur Radiol*. 2009;19:1960-7.

Narin B, Sungurlu F, et al. Comparison of MR enteroclysis with colonoscopy in Crohn's disease--first locust bean gum study from Turkey. *Saudi J Gastroenterol*. 2009;15:253-7.

Crook DW, Knuesel PR, et al. Comparison of magnetic resonance enterography and video capsule endoscopy in evaluating small bowel disease. *Eur J Gastroenterol Hepatol*. 2009;21:54-65.

Tillack C, Seiderer J, et al. Correlation of magnetic resonance enteroclysis (MRE) and wireless capsule endoscopy (CE) in the diagnosis of small bowel lesions in Crohn's disease. *Inflamm Bowel Dis.* 2008;14:1219-28.

Negaard A, Sandvik L, et al. MRI of the small bowel with oral contrast or nasojejunal intubation in Crohn's disease: randomized comparison of patient acceptance. *Scand J Gastroenterol.* 2008;43:44-51.

Masselli G, Casciani E, et al. Comparison of MR enteroclysis with MR enterography and conventional enteroclysis in patients with Crohn's disease. *Eur Radiol.* 2008;18:438-47.

Malago R, Manfredi R, et al. Assessment of Crohn's disease activity in the small bowel with MR-enteroclysis: clinico-radiological correlations. *Abdom Imaging.* 2008;33:669-75.

Bousvaros A, Antonioli DA, et al. "Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America." *J Pediatr Gastroenterol Nutr* 2008; 44(5): 653-674.

Seiderer J, Herrmann K, et al. Double-balloon enteroscopy versus magnetic resonance enteroclysis in diagnosing suspected small-bowel Crohn's disease: results of a pilot study. *Scand J Gastroenterol.* 2007;42:1376-85.

Negaard A, Paulsen V, et al. A prospective randomized comparison between two MRI studies of the small bowel in Crohn's disease, the oral contrast method and MR enteroclysis. *Eur Radiol.* 2007;17:2294-301.

Triester SL, Leighton JA, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease. *Am J Gastroenterol.* 2006;101:954-64.

Masselli G, Vecchioli A, Gualdi GF. Crohn disease of the small bowel: MR enteroclysis versus conventional enteroclysis. *Abdom Imaging.* 2006;31:400-9.

Maccioni F, Bruni A, et al. MR imaging in patients with Crohn disease: value of T2- versus T1-weighted gadolinium-enhanced MR sequences with use of an oral superparamagnetic contrast agent. *Radiology.* 2006;238:517-30.

Gourtsoyiannis NC, Grammatikakis J, et al. Imaging of small intestinal Crohn's disease: comparison between MR enteroclysis and conventional enteroclysis. *Eur Radiol.* 2006;16:1915-25.

Golder SK, Schreyer AG, et al. Comparison of capsule endoscopy and magnetic resonance (MR) enteroclysis in suspected small bowel disease. *Int J Colorectal Dis.* 2006;21:97-104.

Frokjaer JB, Larsen E, et al. Magnetic resonance imaging of the small bowel in Crohn's disease. *Scand J Gastroenterol.* 2005;40:832-42.

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Appendix F Assessment of economic evaluation

CHEERS Assessment of Cipriano (2012) economic evaluation of MR compared to CT

No.	CHEERS criteria	Assessment
1	Identifies the study as an economic evaluation in title and interventions described	✓ p.1240
2	Provides a structured summary of objectives, perspective, setting, methods (study design and inputs) results (base case and uncertainty analyses and conclusions.	✓ p.1240
3	Provides an explicit statement of the broader context of the study. Presents the study question and its relevance for health policy or practice decisions	✓ p.1241
4	Describes characteristics of the base case population and subgroups analysed and why they were chosen	✓ p.1242
5	States relevant aspects of the system in which the decision needs to be made	x
6	Describes the perspective of the study and relates this to the costs being evaluated	✓ p.1241
7	Describes the interventions or strategies being compared and state why they were chosen.	✓ p.1241
8	States the time horizon over which costs and consequences are being evaluated and says why appropriate	✓ p.1241, x
9	Reports the choice of discount rate(s) used for costs and outcomes and says why	✓ p.1242, x
10	Describes what outcomes were used as the measures of benefit and relevance for analysis	✓ Suppl file
11	a) Single-study – describes fully the design features and why single study was sufficient for clinical effectiveness b) Synthesis-based – describes the methods used for identification of included studies and synthesis of clinical effectiveness data	- ✓ Suppl file
12	If applicable, describes the population and methods used to elicit preferences for outcomes	✓ Suppl file
13	a) Single-study – describes fully the approaches to estimate resource use, valuation methods and any adjustments made b) Synthesis-based – describes the methods used for resource use associated with model health states, valuation and adjustments made	- ✓ Suppl file
14	Reports the dates of the estimated resource quantities and unit costs, year reported for unit costs, methods for converting costs into a common currency base and exchange rate	✓ Suppl file
15	Describes and gives reasons for the specific type of decision analytic model used. Illustration is highly recommended.	✓ p.1241
16	Describes all structural or other assumptions underpinning the decision-analytical model.	✓ Suppl file
17	Describes all analytical methods supporting the evaluation (methods dealing with skewed, missing or censored data, extrapolation methods, pooling data and any adjustments) and methods for handing population heterogeneity and uncertainty.	✓ Suppl file
18	Reports the values, ranges, references and if used probability distributions used for all parameters. Reports reasons or sources for distributions used to represent uncertainty. A table showing these is highly recommended	✓ Suppl file
19	Reports the mean values for each intervention, mean values for main categories of costs and outcomes as well as mean differences between comparator groups and incremental cost effectiveness ratio if relevant	✓ Table 1, p.1244
20	a) Single study-based economic evaluation: Describes and effects of sampling uncertainty for the incremental cost and effectiveness estimates and impact of any assumptions b) Model-based economic evaluation: Describes the effects on the results of uncertainty for all input parameters, and related to structure of model and assumptions	- ✓ p.1244-5
21	If applicable, reports differences in costs, outcomes, input parameters that can be explained by variations between subgroups of patients with different baseline characteristics	X n/a

No.	CHEERS criteria	Assessment
22	Summarises key study findings and describes how they support the conclusions reached. Discussed limitations and generalisability of the findings and how they fit with current knowledge	✓ pp1244-47
23	Source of funding and role of funder in study. Describes other non-monetary support	✓ p.1240
24.	Describes any potential for conflict of interest of study contributors in accordance with journal policy	unclear

Glossary and abbreviations

AHMAC	Australian Health Ministers' Advisory Council
AIHW	Australian Institute of Health and Welfare
ANZHSN	Australian and New Zealand Horizon Scanning Network
ARTG	Australian Register of Therapeutic Goods
AR-DRG	Australian Related Diagnosis Related Group
ARPANSA	Australian Radiation Protection And Nuclear Safety Agency
CD	Crohn's disease
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CT	computer tomography
DAP	Decision Analytic Protocol
DHS	Department of Human Services
EQ-5D	EuroQol-5D
FN	false Negative
FP	false Positive
GP	General practitioner
HESP	Health Expert Standing
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
LR	likelihood ratio
MBS	Medical Benefits Schedule
MD	mean difference
MRI	magnetic resonance imaging
MRE	magnetic resonance enterography
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NPV	negative predictive value
PBS	Pharmaceutical Benefits Scheme
PPV	positive predictive value
QALY	quality-adjusted life year
QUADAS	Quality Assessment of Studies of Diagnostic Accuracy Included in Meta-Analyses
RANZCR	Royal Australian and New Zealand College of Radiologists
SBFT	small bowel follow through
TP	true Positive
TN	true Negative

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