

***Assessment of liver
iron by R2-MRI data
analysis***

July 2010

MSAC application 1131

Assessment report

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The Medical Services Advisory Committee (MSAC) is an independent committee 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 by Ms Liliana Bulfone, Ms Sandra Younie and Ms Bridie Murphy from Deakin Health Technology Assessment Group, (DHTAG), Deakin Health Economics, Deakin University, and an Advisory Panel of experts. The report was commissioned by the Department of Health and Ageing on behalf of the Medical Services Advisory Committee (MSAC). It was edited by Mr Dan Goldfarb, Words Editing Services, Victoria.

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Executive summary

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 and Ageing 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.

Summary of the evaluation of assessment of liver iron by R2-MRI data analysis conducted for MSAC

Purpose of application

An application was made to MSAC by Resonance Health Analysis Services Pty Ltd requesting public subsidy, via the Medicare Benefits Schedule (MBS), of FerriScan® for assessment of hepatic iron concentration (HIC) to monitor patients with or at risk of transfusional iron overload.

The intervention involves two components:

- (i) acquisition of R2 data from magnetic resonance imaging (MRI);
- (ii) analysis of R2-MRI data to assess the extent of iron overload in a patient.
FerriScan® is a software application that is used to analyse R2 data from an MRI of a patient's liver.

MRI involves transmission of a radio stimulus into the body. The radio stimulus excites water protons to a higher energy state. As these protons 'relax' back to their unexcited state, they emit signals that are received and interpreted by the MRI scanner. R2 is one of several dimensions used to describe the rate at which protons return to a low energy state.

Although not directly specified in the application, the MBS listing implied by the application could be summarised as presented in Table 1. It is presumed that MRI services could only be provided at eligible locations (consistent with other listings of MRI services).

Table 1: MBS descriptor implied by the application

Category 2 – MISCELLANEOUS DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
<p>MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where:</p> <ul style="list-style-type: none"> - the patient is referred by a specialist or by a consultant physician - the patient has been diagnosed with thalassaemia major or is at risk of transfusional iron overload <p>- scan of liver for assessment of hepatic iron concentration, including computerised analysis of MRI data by FerriScan®</p>
<p>Fee: \$600.00 (includes cost for MRI and data analysis)</p> <p><i>For comparison, the MBS fee, at 1 July 2010, for Item 63482 – MRI scan of the pancreas and biliary tree – is \$403.20; assuming a similar fee for the MRI component of this intervention suggests the applicant is seeking a fee of \$196.80 for the computerised quantitative analysis of data collected by MRI.</i></p>

An independent evaluation team, Deakin Health Economics (DHE), was engaged by the Department of Health and Ageing to conduct an assessment of the intervention for consideration by MSAC. In conducting its assessment of this intervention, the evaluation team received advice from an Advisory Panel with expertise in this therapeutic area.

On the basis of advice from the Advisory Panel, the objective of the assessment to be conducted by the evaluation team was broadened in two ways:

- (i) the intervention of interest was defined as ‘assessment of liver iron by an R2-MRI data analysis system’ (i.e., the assessment was not to be limited to consideration of the FerriScan® commercial product);
- (ii) the population was defined as ‘individuals with, or suspected of, systemic iron overload’.

Thus, in addition to considering use of the technology for patients with transfusional iron overload, the assessment report was to also consider use of the technology for patients with non-transfusional iron overload (e.g., for patients with hereditary haemochromatosis). The essential features of the MBS listing assumed in the assessment could be summarised as presented in Table 2.

Table 2: MBS descriptor initially assumed by assessment report

Category 5 – DIAGNOSTIC IMAGING SERVICES GROUP I5 - MAGNETIC RESONANCE IMAGING SUBGROUP 20 - SCAN OF PELVIS AND UPPER ABDOMEN - FOR SPECIFIED CONDITIONS
<p>MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where:</p> <ul style="list-style-type: none"> - the patient is referred by a specialist or by a consultant physician - the patient has, or is suspected of having, iron overload <p>- scan of liver for assessment of hepatic iron concentration, including computerised analysis of R2-MRI data</p>
<p>Fee: \$600.00 (includes cost for MRI and data analysis)</p>

Following consideration of the evidence base in relation to R2-MRI data analysis for assessment of HIC, the Advisory Panel agreed that the MSAC assessment would benefit from inclusion of a review of evidence for analysis of other dimensions (e.g., R2*, T2,

T2*) used to report relaxation rates following MRI. Furthermore, evidence should not be limited to the use of such technology for assessment of HIC but should include assessment of iron in other organs, particularly the heart. This evidence is summarised in the section of the Executive Summary titled ‘Other relevant factors’ on page xxiv.

Current arrangements for public reimbursement

Currently, there are no MBS items for either of the components required for assessment of iron stores in body organs by analysis of relaxometry data from MRI, neither performance of MRI to measure relaxometry data nor the analysis of data captured by MRI.

Assessment of HIC by R2-MRI data analysis is funded by some hospitals. For example, the application indicates that, at present, the Royal Adelaide Hospital funds up to two assessments per annum of HIC by R2-MRI data analysis (i.e., every six to 12 months) for patients with or at risk of transfusional iron overload.

More commonly, assessment of iron stores in body organs (i.e., not just the liver but also other organs such as the heart) using assessment of relaxometry data (i.e., not just R2 data but also R2*, T2 and T2* data) is conducted in research settings.

Clinical need

Quantifying and monitoring of tissue iron concentrations is important in the clinical management of patients with or at risk of iron overload. Iron overload occurs most often due either to:

- (i) hereditary (primary) haemochromatosis; or
- (ii) due to repeated blood transfusions.

Conditions that are associated with a need for repeated blood transfusions include severe, chronic anaemias, such as haemoglobinopathies (including thalassaemia major) and myelodysplastic conditions.

Regardless of whether iron overload is due to primary haemochromatosis or secondary to repeated blood transfusions, excess iron can accumulate in nearly all tissues and the pattern of organ injury is the same. Most morbidity results from deposition in the liver, endocrine organs, heart, pancreas, and joints. Iron cardiomyopathy is of particular concern, and remains the leading cause of death for patients with thalassaemia major.

The characterisation of iron stores is, therefore, important to prevent and to guide treatment of iron overload.

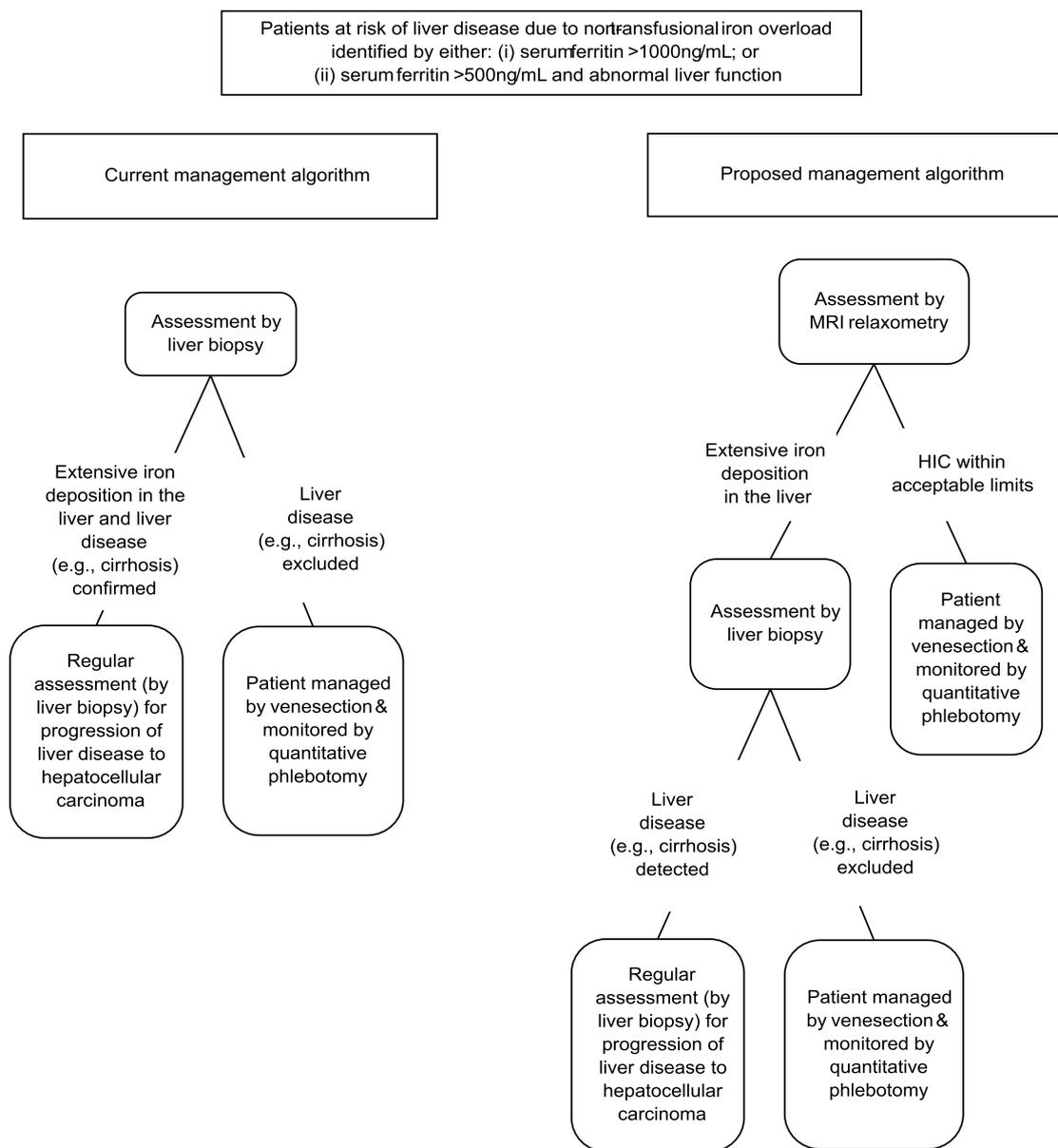
Management algorithms are summarised for:

- (i) patients with primary haemochromatosis (Figure 1); and
- (ii) patients with or at risk of transfusional iron overload (Figure 2).

As shown in Figure 1, for patients with primary haemochromatosis, R2-MRI could be positioned as a screening tool to identify those who should be followed up with liver biopsy. In this scenario, R2-MRI would substitute for an assessment of HIC by chemical

assay of a liver biopsy sample from a patient diagnosed with haemochromatosis. The Advisory Panel advised that patients who are confirmed as having liver disease (e.g., cirrhosis) following MRI would then be managed by regular liver biopsy to monitor for progression of the disease to hepatocellular carcinoma. Patients who are demonstrated to not have liver disease are initiated on treatment with serial quantitative phlebotomy to prevent development of liver disease. For patients with haemochromatosis found to have liver disease, R2-MRI is ultimately an additional test, but for those who do not have liver disease at diagnosis, it substitutes for a liver biopsy. Theoretically, patients newly diagnosed with haemochromatosis should require only a single assessment of R2-MRI to determine their HIC. However, the Advisory Panel advised that the use of R2-MRI data analysis, should it be recommended for inclusion on the MBS, should be permitted once every three years to allow for management of patients who are diagnosed with haemochromatosis, but who are temporarily lost to follow-up or who are non-compliant with the recommended venesection schedule.

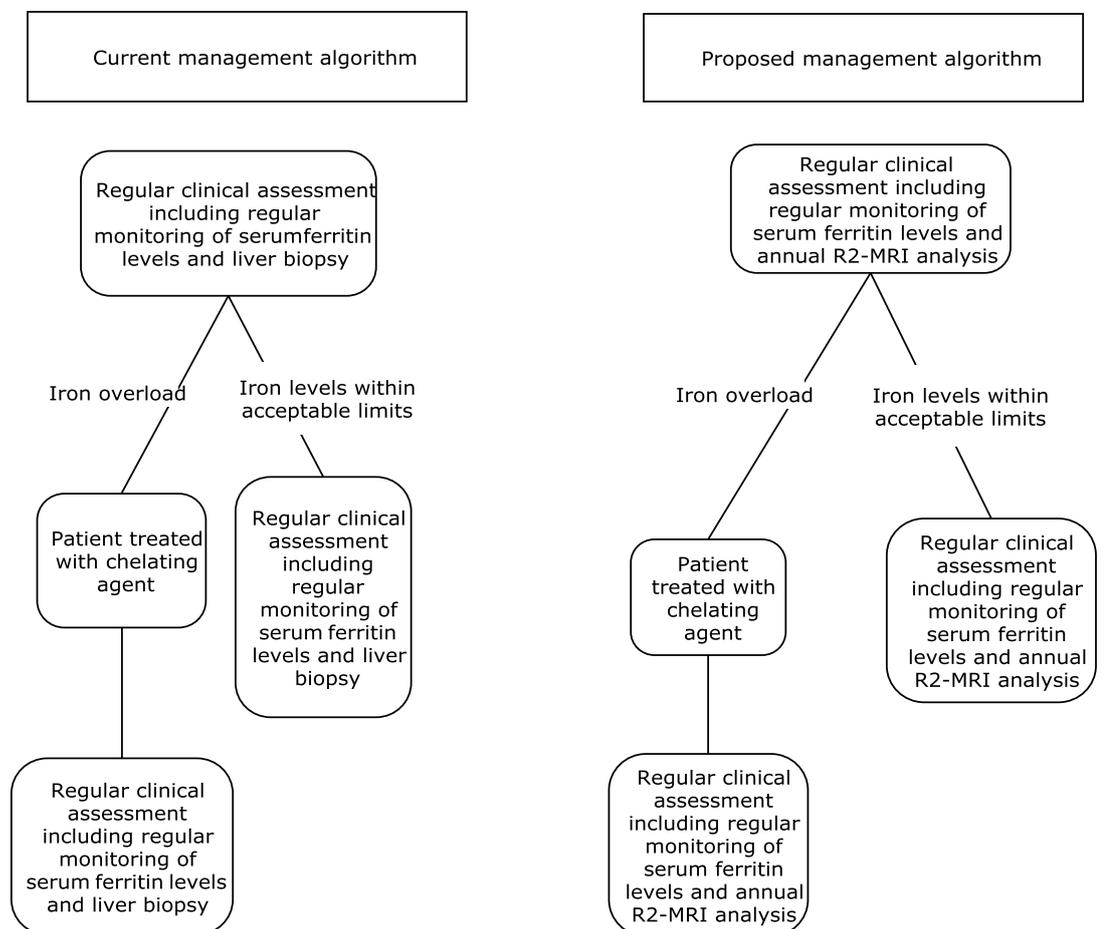
Figure 1: Management algorithm for patients at risk of liver disease due to non-transfusional iron overload



As shown in Figure 2, for patients with or at risk of transfusional iron overload, R2-MRI data analysis could be positioned as a tool to both diagnose iron overload in the liver and monitor change in iron content of the liver over time. According to the algorithm presented, assessment of HIC by R2-MRI data analysis is positioned as a substitute for assessment of HIC by chemical assay of a liver biopsy sample. However, it is notable that substantial numbers of patients at risk of transfusional iron overload do not have regular liver biopsies. In these cases, assessment of HIC by R2-MRI data analysis will be used in addition to the current management and monitoring tools. The Advisory Panel advised that use of R2-MRI data analysis, should it be recommended for inclusion on the MBS, should be limited to once-annually for patients at risk of transfusional iron overload.

Figure 2: Management algorithm for patients with or at risk of transfusional iron overload

- Population with, or at risk of, transfusional iron overload, which primarily consists of:
- children with severe haemoglobinopathies (such as thalassaemia major) who have received >50 units of blood
 - adults with severe haemoglobinopathies (such as thalassaemia major)
 - adults with myelodysplastic disorders with serum ferritin levels >1000ng/L.



Although input will be required from the Schedule Production and Review Section of the Medicare Benefits Branch of the Department of Health and Ageing (DoHA), on the specific wording of MBS item descriptors, the discussions above resulted in refinement of the essential features of the MBS listings assumed by this MSAC assessment report. Effectively, this MSAC assessment considers two listings, the essential features of which can be summarised as presented in Table 3 and Table 4.

Table 3: MBS descriptor for patients with haemochromatosis assumed by assessment report

Category 5 – DIAGNOSTIC IMAGING SERVICES GROUP I5 - MAGNETIC RESONANCE IMAGING SUBGROUP 20 - SCAN OF PELVIS AND UPPER ABDOMEN - FOR SPECIFIED CONDITIONS
MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where: <ul style="list-style-type: none"> - the patient is referred by a specialist or by a consultant physician; - the patient is at risk of liver disease due to non-transfusional iron overload (e.g., patients with primary haemochromatosis) defined by either: <ul style="list-style-type: none"> (i) serum ferritin levels >1000ng/mL; or (ii) serum ferritin levels >500ng/mL and abnormal liver function; - the service has not been performed on the same patient within the previous 36 months; - scan of liver for assessment of hepatic iron concentration, including computerised analysis of R2-MRI data.
Fee: \$600.00 (includes cost for MRI and data analysis)

Table 4: MBS descriptor for patients at risk of transfusional iron overload assumed by assessment report

Category 5 – DIAGNOSTIC IMAGING SERVICES GROUP I5 - MAGNETIC RESONANCE IMAGING SUBGROUP 20 - SCAN OF PELVIS AND UPPER ABDOMEN - FOR SPECIFIED CONDITIONS
MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where: <ul style="list-style-type: none"> - the patient is referred by a specialist or by a consultant physician; - the patient has, or is at risk of, transfusional iron overload, and falls into one of the following classifications: <ul style="list-style-type: none"> (i) children with severe haemoglobinopathies (such as thalassaemia major) who have received >50 units of blood; (ii) adults with severe haemoglobinopathies (such as thalassaemia major); (iii) adults with myelodysplastic disorders with serum ferritin levels >1000ng/mL; - the service has not been performed on the same patient within the previous 12 months; - scan of liver for assessment of hepatic iron concentration, including computerised analysis of R2-MRI data.
Fee: \$600.00 (includes cost for MRI and data analysis)

Comparator

For all patients, R2-MRI data analysis is unlikely to have an impact on the utilisation of indirect methods used to monitor iron levels in the liver (e.g., serum ferritin). Indirect methods are the primary methods for monitoring changes in iron load over short periods (e.g., month to month).

The Advisory Panel considered that, for patients with primary haemochromatosis, analysis of R2 data from MRI scans will replace some liver biopsies. Currently, liver biopsy is indicated for all patients diagnosed with haemochromatosis to:

- (i) assess the extent of iron overload in the liver; and
- (ii) detect liver disease.

Patients with haemochromatosis who have iron overload in the liver are at high risk of liver disease (e.g., cirrhosis). The presence of liver disease has important prognostic implications for risk of hepatocellular carcinoma and survival. It has been assumed that, if R2-MRI data analysis is available on the MBS, patients would, upon diagnosis of haemochromatosis, have HIC assessed by R2-MRI, and then only patients diagnosed with iron overload in the liver would be referred for liver biopsy to test for liver disease.

It is widely accepted that chemical assay of a liver biopsy sample is, currently, the most reliable method for assessing HIC in transfusion-related iron overload (i.e., patients with severe haemoglobinopathies and patients with myelodysplastic conditions). Although assessment of HIC by chemical assay of a liver biopsy sample is desirable and indicated for such patients, the extent to which it is used in practice varies among centres that manage patients with transfusion-related iron overload.

The primary comparator assumed to be relevant in this assessment of R2-MRI data analysis technology is chemical assay of a liver biopsy sample. However, it is acknowledged that for some patients (e.g., those in whom liver biopsy is indicated but not undertaken) the comparator is no assessment of HIC.

Scientific basis for comparison

A literature search found no studies that investigated the implications of inclusion of R2-MRI data analysis (for the purpose of estimating HIC) in algorithms for managing patients at risk of iron overload for final patient outcomes (e.g., survival, quality-adjusted survival). A linked search of the literature was then undertaken to identify studies addressing each of the following questions:

- 1) Is the test safe?

The safety of R2-MRI data analysis can be separated into:

- (i) the safety of the software application; and
- (ii) the safety of MRI scans, particularly, regular repeated MRI scans.

A literature search did not locate any reports that related to studies that addressed the safety of R2-MRI data analysis. Given that R2-MRI data analysis involves the use of a software program with no patient exposure, it is unlikely that there will be any adverse events associated with its use.

The safety of regular MRI scans was assessed by a review of the literature. The references listed in Table 5 were retrieved and were used to assess the safety of MRI, particularly repeated MRI scans.

Table 5: Literature consulted for review of the safety of MRI

Report	Study design and quality appraisal
Hartwig et al., 2009	Review of the effects of non-ionising electromagnetic fields employed in MRI, relevant to patients' and workplace safety.
Formica & Silvestri, 2004	Review of the bio-effects produced by MRI systems acting directly on the human body.
Keevil et al., 2005	Commentary
De Wilde et al., 2007	Case series report. Summarises safety issues and risks associated with exposure to MRI.
Independent Advisory Group on Non-ionising Radiation, Health Protection Agency, 2008	Case series report. Review produced by independent Advisory Group on Non-ionising Radiation summarising mechanisms for interaction, cellular, animal and human studies, trials, and case reports.
Dobson et al., 2009	Analytical observation. Evaluation of cellular effects via nano-magnetic actuation of endogenous iron oxides in human tissue.
Dempsey et al., 2002	Case series report. Review summarising the potential electromagnetic interactions within the MR imaging environment.
Schenck, 2000	Case series report. Review of issues associated with the exposure of patients to strong static magnetic fields during MRI.
Schenck, 2005	Review of proposed interactions of magnetic fields with human tissues.
Schenck et al., 1992	Cross sectional survey of 9 volunteers exposed to whole-body scans at 4T and 1.5T and 24 patients exposed to 1.5T only.
New et al., 1983	Technical report. Evaluation of 21 aneurysm and hemostatic clips, and other biomedical implant materials for longitudinal forces and torques under nuclear magnetic resonance imaging.
Shellock & Crues, 1988	Technical report. Evaluation of the ferromagnetic qualities of 36 different metallic biomedical implants for imaging safety with high-field-strength MR systems.
Shellock, 2002	Case report. Invited review evaluating MR safety and MR compatibility issues for a variety of implants and devices.

2) Is the test accurate?

A literature search located the report of a single study that directly addressed the accuracy of R2-MRI (where R2 assessments are transformed to estimates of HIC assuming the same calibration curve incorporated into the FerriScan® software) when compared with chemical assay of a liver biopsy sample:

- St Pierre TG, Clark PR, Chua-anusom W et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood* 2005; 105:855-861.

3) Does the test change patient management?

The provision of more accurate estimates of HIC has the potential to change how a patient is managed, particularly the details of the administration of chelating agents (choice of agent, mode of administration, dose, frequency, etc.).

The literature search did not locate any reports of studies that addressed this question; however, the application to MSAC requesting subsidy of R2-MRI data analysis did include details of one unpublished study:

- Patton N, Tapp H, Taylor J, Brown G, St Pierre T. The effect of access to non-invasive liver iron concentration measurements on patients at risk of iron overload from multiple blood transfusions: an audit and retrospective study.

4) Does the treatment change health outcomes?

Phlebotomy is the accepted treatment for management of patients with hereditary haemochromatosis, and chelation therapy is the accepted treatment for treating transfusional iron overload. The use of such interventions to manage or prevent iron overload is well established in these conditions. Therapeutic venesection for the management of haemochromatosis is reimbursed under the MBS (MBS Item 13757) and chelating agents (desferrioxamine, deferiprone and deferasirox) are reimbursed under the Pharmaceutical Benefits Scheme (PBS). This assessment assumes that the effectiveness of these therapies is not in dispute and that a change in management to better guide therapy will be associated with improved patient outcomes.

Safety

Key results

Given that R2-MRI data analysis involves the use of a software program with no patient exposure, it is unlikely that there will be any adverse events associated with its use.

MRI does not involve ionising radiation, so it has been generally accepted as a 'safe' imaging modality as long as proper precautions are taken. There is no evidence of a cumulative effect on health as a result of repetitive exposure to magnetic fields.

The strong static magnetic fields used in MRI may pose a risk to patients. The main established hazard of MRI is the so-called 'projectile' or 'missile effect' where, as a result of the large gradient field, ferromagnetic objects that inadvertently enter the field are accelerated and become dangerous projectiles. Most reported cases of MRI-related injuries have been caused by misinformation related to the safety aspects of the magnetic resonance imaging environment. They include projectile and burn incidents, altered device function (e.g., cardiac pacemaker), and the presence of unknown foreign metal objects.

Contraindications for MRI include the presence of internal cardiac pacemakers, implanted cardiac defibrillators, neurostimulators, bone growth stimulators, implanted drug infusion pumps, cochlear implants, ocular implants, metallic vascular access ports, and some aneurysm clips.

Adverse effects that have been associated with MRI include sensory effects such as nausea, vertigo, and metallic taste.

By comparison, liver biopsy is an invasive and painful procedure, and carries the risk of bleeding and infection as well as damage to the liver or surrounding organs. However, fatal complications have rarely been reported. The safety of liver biopsy is enhanced by ultrasound guidance; a complication rate of 0.5% was reported in one large study.

Overall conclusion with respect to safety

Assessment of HIC by R2-MRI data analysis is likely to be associated with safety advantages when compared with assessment of HIC by liver biopsy.

Clinical Effectiveness

Key results - accuracy

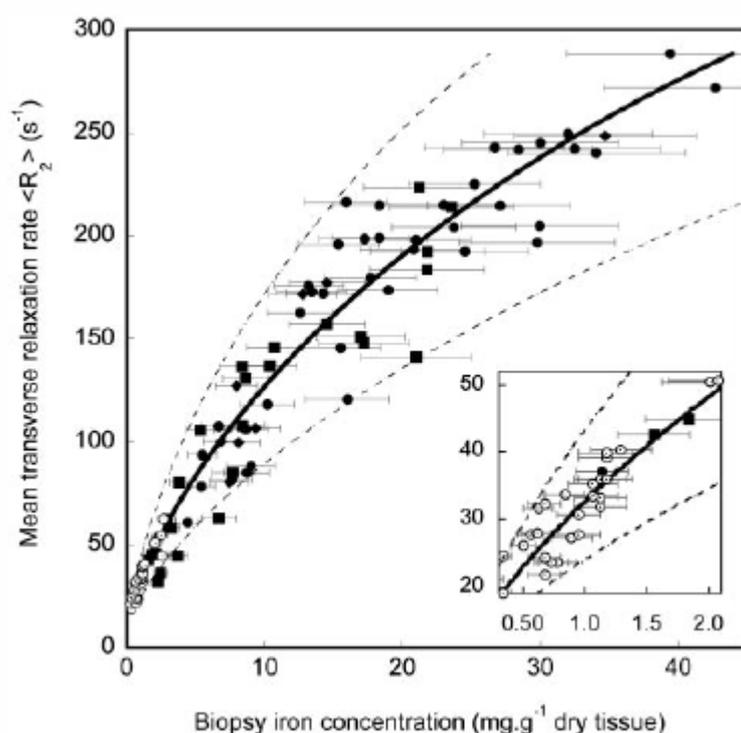
The single study reporting the accuracy of assessment of HIC by R2-MRI data analysis had two purposes:

- (i) derivation of a calibration curve to determine HIC from an R2 value; and
- (ii) comparison of HIC as estimated by R2-MRI data analysis with HIC as estimated by chemical assay of a liver specimen obtained by needle biopsy

The calibration curve in Figure 3 was derived from data from this study to estimate HIC from R2 values. The inset in Figure 3 is a magnification of the lower end of the curve, where results are those generated for subjects that were not iron loaded (i.e., for patients with hepatitis).

On the basis of the calibration curve derived, a specific mathematical relationship is implicitly proposed to exist between an R2 measurement and HIC ($R2 = 6.88 + 26.06[Fe]^{0.701} - 0.438[Fe]^{1.402}$). The FerriScan® software applies this very specific relationship to R2 values to generate estimates of HIC.

Figure 3: R2-HIC calibration curve



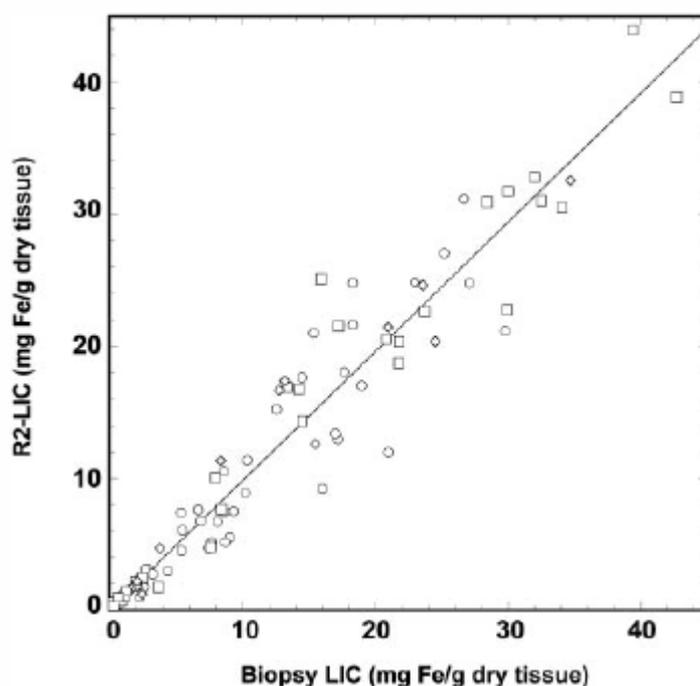
The sensitivities and specificities of the measured liver R2 values for the discrimination of biopsy HIC values above various clinically significant thresholds are summarised in Table 6 along with their 95% confidence limits. The area under the receiver operating characteristic (ROC) plot (along with standard error [SE]) is given for each clinically important HIC threshold, together with an SE calculated by the method of Hanley and McNeil, to give an approximate estimate of the uncertainty on the area.

Table 6: The sensitivity and specificity of liver R2 for biopsy HIC prediction

HIC threshold in mg Fe/g dry weight ($\mu\text{mol Fe/g dry weight}$)	Clinical relevance	Sensitivity (95% CI)	Specificity (95% CI)	Area under ROC plot (SE)
1.8 (32)	Upper 95% of normal	0.94 (0.86-0.97)	1.0 (0.88-1.00)	0.991 (0.008)
3.2 (57)	Suggested lower limit of optimal range for HICs for patients with transfusional iron overload treated with chelation therapy	0.94 (0.85-0.98)	1.00 (0.91-1.00)	0.988 (0.010)
7.0 (125)	Suggested upper limit of optimal range for HICs for patients with transfusional iron overload beyond which there is an increased risk of iron-induced complications	0.89 (0.79-0.95)	0.96 (0.86-0.99)	0.991 (0.009)
15.0 (269)	Threshold for greatly increased risk for cardiac disease and early death in patients with transfusional iron overload.	0.85 (0.70-0.94)	0.92 (0.83-0.96)	0.982 (0.0016)

Figure 4 compares the HIC values estimated using R2-MRI data analysis with the HIC values estimated by chemical assay of a liver sample collected by needle biopsy. The R2-HIC values are derived using the calibration curve shown in Figure 3. The solid line is a straight line fitted through the origin and has a gradient of 0.980 ± 0.018 . The different data symbols differentiate between the different fibrosis stages: stages 0 and 1, \circ ; stages 2 to 4, \square ; and stages 5 and 6, \diamond .

Figure 4: R2-HIC versus biopsy HIC as reported by St Pierre et al., 2005



Key uncertainties - accuracy

The following uncertainties were noted with respect to the evidence concerning accuracy of assessment of HIC by R2-MRI data analysis compared with liver biopsy:

- St Pierre et al. use the same set of data to:
 - derive a calibration curve to convert average R2 measurements to an HIC (as shown in Figure 3); and
 - to compare the HIC values estimated using R2-MRI data analysis with the HIC values estimated by chemical assay of a liver sample collected by needle biopsy (as shown in Figure 4).

The Advisory Panel considered that although the derived calibration curve could form the basis for a hypothesis of the relationship between HIC and R2 values, for the validity of the relationship to be accepted, assessments of HIC by liver biopsy and by R2 should be conducted in a separate group of patients and the same relationship found to apply.

- It does not appear that sufficient investigation has been conducted into whether the calibration curve is applicable to patients in various relevant subgroups; e.g., patients with hereditary haemochromatosis versus patients with transfusional iron overload; adults versus children; across different levels of fibrosis; patients on chelation therapy versus those not on chelation therapy.

Key results – impact on patient management

Patton et al. report the results of a retrospective audit of the medical records of all patients referred to the Radiology Department of the Royal Adelaide Hospital for assessment of HIC by R2-MRI data analysis. The referrals were from within the Royal Adelaide Hospital and from the Women's and Children's Hospital.

Table 7 summarises the results reported by Patton et al.

Table 7: Results reported by Patton et al.

Outcome	At initial FerriScan® N = 40	At final FerriScan® N = 40	Difference
Chelation therapy at time of initial R2-MRI scan			
• No therapy	7	2	-5
• Desferrioxamine	33	16	-17
• Desferrioxamine & deferiprone		1	+1
• Deferasirox		20	+20
• Desferrioxamine & deferasirox		1	+1
HIC by R2-MRI analysis			
- Geometric mean in mg Fe/g dry tissue (range)	6.8 (0.5-41.3)	4.8 (0.9-40.1)	-2.0 (p = 0.008)
Proportion of patients with HIC by R2-MRI:			
> 15 mg Fe/g dry tissue	14/40 (35%)	5/40 (12.5%)	-22.5% (p = 0.01)
> 7 mg Fe/g dry tissue	20/40 (50%)	14/40 (35%)	-15% (p = n.s.)
Serum ferritin levels			
- Geometric mean in µg/L (range)	1502 (253-9940)	1389 (266-4291)	-113 (p = n.s.)
Serum ferritin levels*			
> 2500 µg/L	11/40 (25%)	11/40 (25%)	0 (p = n.s.)
> 1500 µg/L	18/40 (45%)	19/40 (47.5%)	+2.5% (p = n.s.)
12 month averaged serum ferritin levels#			
- Geometric mean µg/L (range)	1541 (243-9903)	1442 (239-5157)	-99 (p = n.s.)
12 month averaged serum ferritin levels #			
> 1500 µg/L	18/40 (45%)	17/40 (42.5%)	-2.5% (p = n.s.)
> 2500 µg/L	10/40 (25%)	12/40 (30%)	+5% (p = n.s.)

n.s. = non-significant

* Those closest to R2-MRI measurement used but only if within 30 days (162 pairs of HIC and SeFe available for comparison)

12 month period immediately preceding 1st R2-MRI analysis and immediately preceding the final R2-MRI data analysis were calculated where values were available

A total of 19 clinical decisions were documented in the case notes as being based on HIC results. These decisions comprised initiation of chelation therapy, increasing chelator dose, decreasing chelator dose, and change of mode of delivery of desferrioxamine from subcutaneous to intravenous.

On the basis of results presented above, Patton et al. claim that the significant decreases in the body iron burden, together with the documented clinical decisions regarding chelation therapy based on the HIC results, support the following hypothesis: Introduction of non-invasive monitoring of HIC can lead to a decreased body iron burden through improved clinical decision making and improved feedback to patients, and hence improved adherence to chelation therapy. The study authors also conclude that the inability of serum ferritin measurements to detect the drop in body iron burden of the cohort is most likely due to the test's poor sensitivity and specificity of serum ferritin concentration.

Key uncertainties – impact on patient management

The following uncertainties were noted with respect to the evidence concerning the impact of availability of assessments of HIC by R2-MRI data analysis on patient management:

- The study conducted by Patton et al. has several design limitations which are likely to result in substantial confounding to the interpretation of results:

- The study does not include information for a comparator arm; it is not possible to determine what results would have been observed in the absence of HIC by R2-MRI. It is therefore not possible to determine whether the observed changes in HIC and chelation therapy are due solely to patients receiving R2-MRI data analysis to guide their treatment, or due to other reasons. It is possible that the same clinical decisions would have been made on the basis of serum ferritin results and clinical assessment (e.g., changes in symptomatology).
- Specific changes made to a patient's management are not documented in either the report nor the spreadsheet provided by the sponsor that records individual patient records (e.g., increase dose of chelator, decrease dose of chelator, change chelator).
- The study results are potentially confounded by:
 - Changes in patient education efforts;
 - Changes in the availability of chelating agents. It is notable that no patients were being treated with deferasirox at the start of the study but several patients commenced therapy with deferasirox (21/40) over the course of the study. Deferasirox became available as a PBS benefit in December 2006. The data collection for this study related to the period between 31 December 2001 and 8 April 2008. It is possible that several patients switching to deferasirox were previously non-compliant with recommended therapy, and the new availability of deferasirox led to an improvement in their management.

Overall conclusion with respect to effectiveness

It appears that, as demonstrated by Table 6, assessment of HIC by R2-MRI data analysis can be used to provide a reliable indication of the range within which the true HIC is likely to lie. The Advisory Panel noted that the same conclusion would be applicable to chemical assay of a liver biopsy sample.

The evidence available is insufficient to reliably conclude that the estimation of hepatic iron concentration values generated by the FerriScan® technology is accurate in measuring HIC in an absolute sense. There is substantial uncertainty regarding the validity of the assumed specific mathematical relationship assumed to exist between R2 and HIC by the FerriScan® software program. The benefit to clinicians of converting R2 values to HIC has to be weighed against the potential for false confidence in the accuracy of the HIC value generated. The Advisory Panel advised that specification of reference ranges for R2 would be more helpful than conversion of R2 values to HIC. For example, values of R2 up to $x s^{-1}$ are normal; values of R2 above $y s^{-1}$ indicate that the patient should commence treatment with chelation therapy; and values of R2 above $z s^{-1}$ indicate that the patient is at increased risk of iron overload-associated complications. Specification of reference ranges for R2 would be consistent with the approach adopted for measurements of other relaxometry metrics (e.g., T2*, which is not converted to an equivalent tissue iron concentration but rather reported in units of s^{-1} and the result compared against a set of reference ranges). The Advisory Panel noted that potential difficulties arose because different approaches may generate different values for R2, such that different reference ranges might apply depending on the approach to the determination of R2. This could potentially cause confusion in practice. However, the

Advisory Panel also noted that there are many precedents for different assays to measure the same parameter with different reference ranges.

It may be likely that more accurate information about liver iron concentration would result in more appropriate management of patients (e.g., more appropriate dosing of chelation therapy, closer surveillance of high-risk patients). However, there is currently no evidence available that convincingly demonstrates or quantifies the extent to which that use of analysis of R2 data to assess the extent of iron overload in a patient will change the patient's management.

Economic evaluation

Assessment of HIC by R2-MRI data analysis will generally substitute for assessment of HIC by chemical assay of a liver biopsy sample. The conduct of cost-effectiveness was not feasible due to lack of information permitting extrapolation of results to patient-relevant outcomes. A comparative cost analysis of the two procedures is presented.

For patients who currently do not have assessment of liver iron by liver biopsy but who might have assessment by R2-MRI data analysis, it was considered that, if R2-MRI data analysis was found to be less costly than liver biopsy, then it would be reasonable to assume that R2-MRI data analysis is acceptably cost-effective. This is based on the grounds that liver biopsy is indicated in these patients and could theoretically be used.

Costs associated with assessment of HIC by R2-MRI data analysis

A cost of \$600.00 per assessment of HIC by R2-MRI data analysis is assumed. For comparison, the MBS fee, at 1 July 2010, for Item 63482 – MRI scan of the pancreas and biliary tree – is \$403.20. Assuming a similar fee for the MRI component of this intervention suggests the applicant is seeking a fee of \$196.80 for the computerised quantitative analysis of data collected by MRI.

With FerriScan®, a telemedicine model is adopted whereby data are transmitted to a central data analysis facility as a digital specimen to be analysed. Following analysis at the central facility, a report detailing results is returned to the radiologist at the centre where the MRI was conducted. Alternate approaches might involve the distribution of software (e.g., by licence) to individual MRI centres for direct use by individual radiologists to assess HIC by R2-MRI data analysis. The latter approaches may be associated with lower costs for analysis of R2-MRI data.

It is assumed that there would be marginal difference between the MBS schedule fee for assessment of HIC by R2-MRI data analysis and the fee charged in practice. This assumption is made on the grounds that the average government cost for MBS Item 63482 – MRI scan of the pancreas and biliary tree – is \$344.41, which is approximately 85.4% of the schedule fee.

Some additional costs may be incurred for patients requiring sedation (MBS Item 63494 with an associated fee of \$44.80) or anaesthesia (MBS Item 63497 with an associated fee of \$156.80). No information was available in the public domain or in the application to MSAC to determine the extent to which these associated items would be used.

Costs associated with assessment of HIC by chemical assay of a liver biopsy sample

Table 8 summarises the MBS items that are likely to be associated with assessment of HIC by chemical assay of a liver biopsy sample. It is notable that, although the safety of liver biopsy is enhanced by ultrasound guidance, no specific MBS item for ultrasound-guided liver biopsy is included. In practice, it is likely that the procedure would be performed with ultrasound guidance. The costs for ultrasound guidance were estimated assuming MBS Item 55036 would be applicable. Costs to the MBS for chemical assay of a liver biopsy sample are likely to be approximately \$345.10. This is estimated by assuming delivery of one of each of the services listed in Table 8 and assuming the average MBS expenditure per item as incurred in 2009. According to calculations of MBS expenditure per item, it appears that anaesthetic services are associated with safety net impact but the impact from the safety net for items is more marginal.

Liver biopsy is generally performed under sedation in a hospital; therefore, costs associated with hospitalisation also need to be taken into account when taking a health care system perspective. The average cost for a liver biopsy performed in hospital on a day-stay basis, without radiological guidance, has been estimated to be \$1032.00 at Liverpool Hospital, South Western Sydney Area Health Service.

Table 8: MBS items associated with chemical assay of a liver biopsy sample

Item	Description and fee ^A	MBS expenditure in 2009	MBS services in 2009	Average expenditure per service in 2009
20702	Initiation of management of anaesthesia for percutaneous liver biopsy (4 basic units) Fee: \$73.20	\$14,949	158	\$94.61
30409	Liver biopsy, percutaneous (Anaes.) Fee: \$161.20	\$312,904	2,437	\$128.40
55036	ABDOMEN, ultrasound scan of, including scan of urinary tract when undertaken but not being a service associated with the service described in item 55600 or item 55603, where: (a) the patient is referred by a medical practitioner for ultrasonic examination not being a service associated with a service to which an item in Subgroups 2 or 3 of this Group applies; (b) the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member; and (c) the service is not performed with item 55038, 55044 or 55731 on the same patient within 24 hours (R) Fee: \$111.30	\$55,878,102	579,997	\$96.34
66831	Quantitation of copper or iron in liver tissue biopsy Fee: \$31.15	\$2,240	87	\$25.75

^A Source: August 2009 Medicare Benefits Schedule

Overall conclusion with respect to cost-effectiveness

Assessment of HIC by R2-MRI data analysis is likely to be cost-saving from a health care perspective compared with assessment of HIC by chemical assay of a liver biopsy sample.

However, since costs of hospitalisation are not borne by the MBS, the assessment of HIC by R2-MRI data analysis is likely to be more costly to the MBS than chemical assay of a liver biopsy sample.

Financial/budgetary impacts

The prevalence of haemochromatosis in a sample of healthy individuals in Australia has been reported to be at least 0.36%, or 1:284 individuals. Extrapolating to an Australian population of 22,000,000, it can be estimated that approximately 77,500 Australians have haemochromatosis. It has been suggested that approximately 60% of patients (which corresponds to 46,500 Australian patients) with hereditary haemochromatosis will eventually develop iron overload. However, a substantial proportion of patients will be undiagnosed because no screening program is in place to detect hereditary haemochromatosis. In the year ending 31 December 2009, 51,250 tests (MBS Item 73317) for the genetic mutation associated with haemochromatosis were performed on patients at high risk for haemochromatosis. Unfortunately, the risk of disease for those with a genetic predisposition has not been elucidated in the literature. Powell et al. (2006) report that screening for haemochromatosis was offered to relatives of 259 patients with proven C282Y-associated haemochromatosis. Unfortunately, the authors do not report the total number of relatives tested. They do report that 401 relatives were identified as being homozygous for the genetic mutation for haemochromatosis and that 69 (17%) of these demonstrated a disease-related clinical condition. In a similar study reported by Bulaj et al. (2000), 25% of identified subjects demonstrated at least one disease-related condition. Assuming the average number of relatives tested per patient with proven haemochromatosis was between 5 and 50, an incidence of genetic mutation of between 3% ($401/(259 \times 50)$) and 30% ($401/(259 \times 5)$) can be estimated for a high-risk population. Applying these proportions, it can be estimated that the number of patients likely to be diagnosed with haemochromatosis and demonstrating some clinical condition per year in Australia will be between 265 ($51,250 \times 3\% \times 17\%$) and 3850 ($51,250 \times 30\% \times 25\%$).

No reports of the prevalence of haemoglobinopathies requiring regular transfusion (e.g., thalassaemia major) in the Australian population were located. However, the Advisory Panel suggested that there would be approximately 500 patients with haemoglobinopathies in Australia who would have a need for regular monitoring of HIC.

Most patients with myelodysplastic syndromes (MDS) are elderly (median age range 65 to 70 years). As a consequence, the incidence and prevalence of these diseases are rising as the population ages. The incidence of MDS from 2001 to 2003 was 3.3 per 100,000 in the USA. Assuming a survival rate of 45% at three years, a prevalence of approximately 10 per 100,000 can be estimated. This suggests that, in an Australian population of 22,000,000, approximately 2,200 patients are affected by MDS. The prevalence of iron overload in patients with MDS is not well described. List (2010) reports that between 50% and 80% of patients with MDS receive transfusions. Patients with higher risk MDS are more frequently dependent upon transfusions than patients with lower risk MDS (68% vs 22%). However, patients with lower risk MDS may survive five years or longer,

and with time may be at greater risk of iron overload. Assuming 50% of MDS patients are at risk of transfusional iron overload, it can be estimated that approximately 1,100 patients would be candidates for monitoring of HIC.

In total, considering patients with haemochromatosis, patients with haemoglobinopathies and patients with MDS, the likely number of patients per year to have assessment of HIC by R2-MRI data analysis is estimated to be between 1,865 and 5,450 (assuming restrictions on frequency of use as included in Table 3 and Table 4). Assuming a cost of \$600.00 per year for assessment of HIC by R2-MRI data analysis, the total financial implications of making this intervention available on the MBS is estimated to be between \$1.1 million and \$3.3 million. It is assumed that there would be little difference between the MBS fee and the fee charged in practice. This assumption is made on the grounds that the average government cost for MBS item Item 63482 – MRI scan of the pancreas and biliary tree – is \$344.41, which is approximately 85.4% of the scheduled fee of \$403.20. Taking only the MBS perspective and assuming negligible impact from the safety net, the financial implications for the MBS could be estimated to be between \$0.9 million and \$2.8 million. No cost-offsets for reduced use of liver biopsy are included in these calculations.

Some additional costs may be incurred for patients requiring sedation (MBS Item 63494 with an associated fee of \$44.80) or anaesthesia (MBS Item 63497 with an associated fee of \$156.80). No information was available to determine the extent to which these associated items would be used.

Other relevant factors

The Advisory Panel indicated that the potential for the availability of other software packages to assess HIC by analysis of MRI relaxometry data was a matter that MSAC needed to consider, especially as other models for providing this service might have advantages in terms of cost-effectiveness of the technology.

The Advisory Panel noted there are other relaxometry methods currently being used for assessment of iron overload in Australia in the research setting. Software to enable assessment of cardiac iron concentration and HIC using analysis of T2*/R2* MRI data were considered to have substantial potential. The Advisory Panel noted that an MRI for assessment of liver iron takes approximately 30 minutes when R2 data is collected but takes 20 minutes when T2* is collected.

The extent of iron overload in cardiac tissue is an important factor affecting treatment decisions for patients with haemoglobinopathies. T2* MRI data analysis methods can be used to assess the extent of iron overload in both liver and the heart. T2 takes only an extra five minutes (compared with R2-MRI) for capture of T2* MRI data to permit both assessments.

As discussed, FerriScan® uses a telemedicine model whereby data are transmitted to a central data analysis facility as a digital specimen to be analysed. Following analysis at the central facility, a report detailing results is returned to the radiologist at the centre where the MRI was conducted. Alternate approaches might involve the distribution of software (e.g., by licence) to individual MRI centres for direct use by individual radiologists to assess HIC by analysis of MRI relaxometry data. The latter approaches may be associated with lower costs.

In order to inform MSAC of the comparative performance of various approaches to assessment of HIC using MRI relaxometry data, a brief review of the evidence for those approaches was conducted. It is detailed in the section titled ‘Other potentially relevant technologies’.

Overall, the evidence for assessment of HIC by R2-MRI data analysis is not more convincing than evidence for assessment of iron stores by data analysis of other MRI relaxometry methods.

The Advisory Panel proposed that, if MSAC recommends the technology be subsidised, the descriptor should be broadened to allow other types of MRI relaxometry methods and to allow the assessment of cardiac iron stores. This could be achieved by changing the descriptors shown in Table 3 and Table 4 from ‘scan of liver for assessment of hepatic iron concentration, including computerised analysis of R2-MRI data’ to ‘scan of liver and/or heart for assessment of iron concentration, including computerised analysis of MRI relaxometry data’.

Introduction

MSAC evaluates new and existing health technologies and procedures, for which funding is sought under the Medicare Benefits Schedule (MBS) 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.

An application was made to MSAC by Resonance Health Analysis Services Pty Ltd requesting public subsidy, via the MBS, of a commercial R2-MRI data analysis system, FerriScan®, for routine measurement of hepatic iron concentration to monitor patients with thalassaemia major, and other patients at risk of transfusional iron overload. Although not directly specified in the application, the MBS listing implied by the application could be summarised as presented in Table 9.

Table 9: MBS descriptor implied by the application

Category 2 – MISCELLANEOUS DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
<p>MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where:</p> <ul style="list-style-type: none"> - the patient is referred by a specialist or by a consultant physician; - the patient has been diagnosed with thalassaemia major or is at risk of transfusional iron overload; - scan of liver for assessment of hepatic iron concentration, including computerised analysis of MRI data by FerriScan®.
<p>Fee: \$600.00 (includes cost for MRI and data analysis) <i>For comparison the MBS fee, at 1 July 2010, for Item 63482 – MRI scan of the pancreas and biliary tree – is \$403.20; assuming a similar fee for the MRI component of this intervention suggests the applicant is seeking a fee of \$196.80 for the computerised quantitative analysis of data collected by MRI.</i></p>

An independent review of the assessment of hepatic iron concentration (HIC) by R2-MRI data analysis in patients with or at risk of systemic iron overload is presented in this report.

This technology involves the use of two components:

- (i) acquisition of MRI data (currently no item on the MBS provides for subsidised MRI of the abdomen for purposes of assessing iron content of the liver); and
- (ii) analysis of R2 data captured by the MRI to estimate iron concentration in the liver

MRI involves transmission of a radio stimulus into the body. The radio stimulus excites water protons to a higher energy state. As these protons ‘relax’ back to their unexcited state, they emit signals that are received and interpreted by the MRI scanner. R2 is one of several dimensions used to describe the rate at which protons return to a low energy state.

Consistent with MSAC’s standard approach, the assessment provided in this report does not consider the merits of a specific commercial product. Instead, the report provides an

assessment of the 'generic' product. This is appropriate because any relevant MBS item descriptor would describe the service in a generic manner and would not specify a particular proprietary product. This is to ensure that if other equivalent technologies enter the market (with regulatory approval) they would not require a separate MSAC assessment. Furthermore, in addition to considering the use of this technology for patients at risk of transfusional iron overload, this MSAC assessment also considers the use of this technology for patients at risk of non-transfusional iron overload. It is acknowledged that, at present, FerriScan® is the only system approved by the Therapeutic Goods Administration (TGA) for delivering this service in Australia.

This report summarises the assessment of current evidence for R2-MRI data analysis for the estimation of the iron concentration in the liver of individuals with, or suspected of, systemic iron overload. The report is to inform a decision as to whether such a technology should be subsidised under the MBS.

Background

Intervention name

R2-MRI analysis system (FerriScan®)

The technology

The R2-MRI analysis system (FerriScan®) is a software application that is used to analyse data from an MRI of a patient's liver. Firstly, spin-echo (R2) images of the scanned object are generated. From these images, an average R2 value for the liver is generated. Using a calibration curve, the software application then converts this average R2 value for the liver to an average hepatic iron concentration (HIC).

The entire process of measuring HIC by means of this system involves four steps:

1. The patient spends approximately 20 minutes in the MRI instrument. No contrast agent is administered.
2. Image data are transmitted electronically to the FerriScan® Service Centre (operated by Resonance Health Analysis Services Pty Ltd) through a secure internet link.
3. The service centre uses a patented methodology for processing the MRI images to generate an estimate of the HIC for the patient.
4. A report that includes an estimate of the HIC for the patient is made available to the MRI centre through the secure link within two working days.

Magnetic resonance imaging (MRI)

MRI involves transmission of a radio stimulus into the body. The signal that is returned after interacting with the body is used to create an image.

MRI does not image the iron stored in tissue directly but instead images protons in hydrogen atoms contained in water molecules. A transmitted radio stimulus is applied to excite protons in water molecules in the body to higher energy states. As these protons 'relax' back to their unexcited state, they emit signals ('echo') that are received and interpreted by the MRI scanner. It has been shown that the 'relaxation rate' of water protons is proportional to the concentration of paramagnetic ions (such as iron)¹.

There are two fundamentally different methods to generate MRI images used for iron quantitation:

- a 'spin echo' pulse sequence may be applied to excite water molecules; or
- a 'gradient echo' pulse sequence may be applied to excite water molecules.

In spin-echo imaging, a 90° excitation pulse is followed by a second 180° 'refocusing' radiofrequency pulse. In contrast, in the case of gradient-echo imaging, a single and smaller excitation pulse (e.g., 15°) is applied.

The decline in the 'echo' (i.e., time for the protons to return to their low energy state) following application of a pulse follows a pattern similar to radioactive decay such that

echo times can be characterised by a half-life constant. In spin-echo imaging, the half-life is known as T2 whereas it is known as T2* in the case of gradient-echo imaging. Often, this variable is presented in the form of a relaxation rate, R2 or R2*. The relaxation rates are simply the reciprocal of the time constants such that $R2 = 1000/T2$ and $R2^* = 1000/T2^*$. The factor of 1000 is included when T2 and T2* are expressed in milliseconds (ms) and relaxation rates are expressed in Hertz (or seconds⁻¹). Areas where the relaxation rate is longer (i.e., it takes longer for the water protons to return to their low-energy state) appear darker in images produced by MRI. The greater the iron content of the tissues, the faster the rate of darkening.²

This report relates to the analysis of R2 data generated by MRI to estimate iron concentration in the liver of individuals with, or suspected of, systemic iron overload.

Analysis of R2 data from MRI scan to determine iron concentration in the liver

There are three main components, as illustrated in Figure 5, to the analysis system used to estimate HIC from R2 data generated by an MRI:

1. In order to ascertain that the MRI scanner is correctly set up for accurate R2 imaging, a set-up protocol and a set of 'phantoms' (called the FerriScan Phantom Pack) are provided to the MRI centre. The phantom pack consists of a series of vials, each containing a known concentration of aqueous manganese chloride (MnCl₂). The concentrations of MnCl₂ range from 0.2 mM to 3.2 mM, a range designed to cover the R2 values found in normal and iron-loaded livers. Solutions of manganese chloride are used to verify the values of R2 because R2 is linearly correlated with manganese concentration.

The MRI centre then determines the specific scanning protocol that should be applied given the MRI scanner platform being used. The MRI centre then scans each of the phantoms in the FerriScan Phantom Pack and forwards the MRI images to the FerriScan® Service Centre.

The FerriScan® Service Centre confirms that the correct R2 measurements are generated for each phantom and thereby confirms that the scanning protocol has correctly been established by the MRI centre.

The MRI centre is then able to scan patients.

2. Raw image data collected by MRI for individual patients is sent by the MRI centre to the FerriScan® Service Centre. There, patented software (ImageR2) is used to analyse the data to generate measurements of R2 across the patient's liver and an R2 image for the largest appropriate axial image slice of the liver is generated. The manufacturer of the software claims (on p. 8 of the application requesting inclusion of this technology on the MBS) that the software appropriately manages a number of considerations, including:

- the change (drift) in imaging gain between successive spin-echo measurements (determined with the aid of a long external reference medium that is scanned with the patient [usually a 1L bag of Hartmann's solution for infusion]);
- the effects of thermal and structured noise originating from both the instrument and the patient on the non-zero baseline noise distribution of the magnitude image data;
- noise filtering necessary for reliable calculation of the relaxation parameters;

- the curve fitting procedure for calculation of accurate relaxation parameters where a small number of spin-echo images are available for analysis.
3. An add-on software module is used to estimate HIC from the R2 image. The software uses a calibration curve to convert the average R2 value for the liver slice to an estimate of average HIC for the liver.

The final product of the FerriScan Analysis System is a report that details the patient's R2 measurements and derived HIC. A sample report is provided in Figure 6.

Figure 5: Key components of the R₂-MRI analysis system

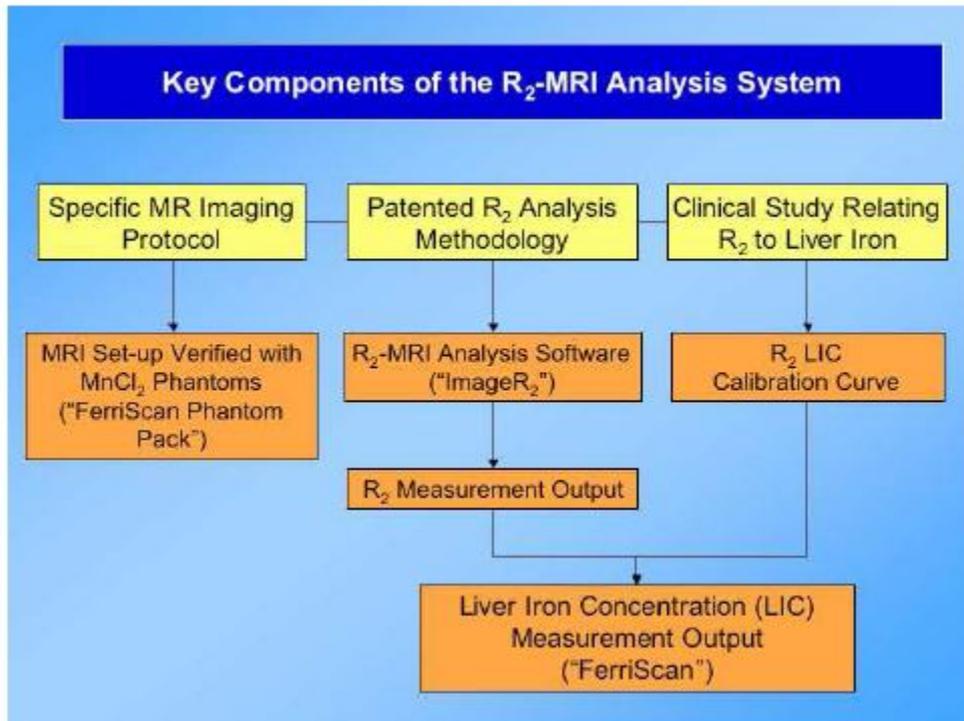
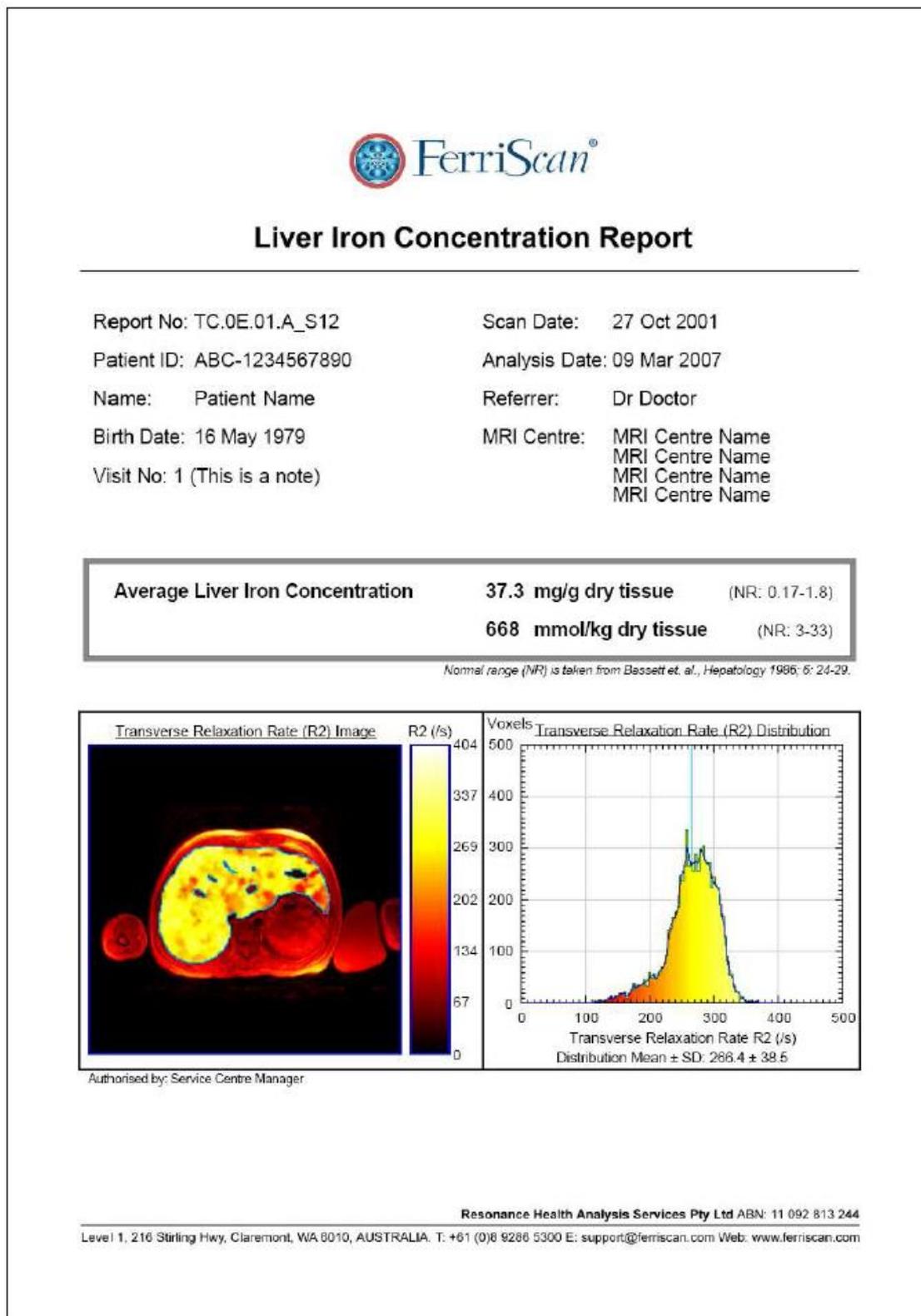


Figure 6: Sample of FerriScan output report



Medicare items are required to be delivered by approved providers but it is unclear whether a radiologist (or some other approved provider) would endorse the results generated by the FerriScan Service Centre. There is no scope under current Medicare provisions for payments to be made to non-approved entities (e.g., directly to Resonance

Health Analysis Services, which processes the FerriScan images off-site). The Advisory Panel considered that the appropriate mechanism for reimbursement would be the parallel to that of the referred pathology test, where the pathology provider subcontracts to a company accredited by the National Association of Testing Authorities, Australia (NATA) and the pathologist ultimately endorses the report. It was agreed that, should this service be made available on the MBS, reimbursements should be paid directly to the radiologist for the MRI and the fee should include a minor component to cover the cost of applying relaxometry analysis techniques to the MRI image. The radiologist would then have the responsibility for choosing from available TGA-approved/accredited options for delivering relaxometry techniques (e.g., by payment to a third-party provider such as Resonance Health Analysis Services Pty Ltd or by direct use of a licenced software program).

Intended purpose

The intended purpose of R2-MRI data analysis is to estimate the iron concentration in the liver of individuals with or suspected of systemic iron overload.

Clinical need

The quantitation and monitoring of tissue iron concentrations is important for the clinical management of patients with or at risk of iron overload.

Total body iron content is normally about 40 mg/kg of body weight in women and approximately 50 mg/kg in men³. In normal individuals, most of the iron in the body is contained in haemoglobin, with smaller amounts found in myoglobin. Iron not required for these purposes is stored in iron storage protein compounds – either in the form of ferritin or haemosiderin. For patients with iron overload, total body iron content is substantially elevated. Increased body iron stores are associated with greater accumulations of these iron-containing proteins. The body is capable of storing relatively large quantities of iron in ferritin and haemosiderin apparently without undue effects, but when the iron load is very heavy or when the storage capacity has been exceeded, tissue damage may ensue.

Iron overload occurs most often due to either:

- (i) hereditary (primary) haemochromatosis; or
 - (ii) due to repeated blood transfusions.
- Primary (hereditary) haemochromatosis is a genetic disorder of iron metabolism that is characterised by excessive iron accumulation causing tissue damage. The mechanism for iron overload in patients with primary haemochromatosis is increased iron absorption from the gastrointestinal tract, leading to chronic deposition of iron in the tissues. Symptoms of iron overload do not develop until organ damage, often irreversible, develops. Symptoms include fatigue, hepatomegaly, bronze skin pigmentation, loss of libido, arthralgias, and manifestations of cirrhosis, diabetes, or cardiomyopathy. Diagnosis is based on serum iron studies and gene assay. Treatment of primary haemochromatosis is with serial phlebotomies.
 - Secondary iron overload may be defined as a group of disorders in which iron overload is attributable to some abnormality other than a primary increase of intestinal iron absorption. The most common cause of secondary iron overload is a

consequence of repeated blood transfusions (transfusional iron overload). Conditions that are associated with a need for repeated blood transfusions include severe, chronic anaemias such as haemoglobinopathies (including thalassaemia major), and myelodysplastic conditions. Each unit of transfused blood typically contains 200–250 mg of iron. Iron accumulation from repeated transfusion occurs as a consequence of the physiological retention of iron from the transfused red cells after they become senescent and are destroyed. No significant physiological means of iron excretion exists. As a result, the element accumulates in the body's tissues. Symptoms and signs of iron overload affecting endocrine, hepatic, and cardiac function are common after 100 units of blood have been transfused (total body iron load of 20g). Chronically transfused patients are typically treated with iron chelation therapy to prevent deleterious consequences of iron overload. Iron chelators currently available include desferrioxamine, which is administered subcutaneously or intravenously, and deferiprone and deferasirox, which are administered orally. Desferrioxamine has a short half-life, and therefore is required to be administered by pump almost continuously (8-12 hrs per day for 5-7 days per week). This administration schedule can lead to poor compliance. Deferiprone can be administered orally three times a day but is less effective than desferrioxamine. Deferiprone has largely been superseded by deferasirox. Deferasirox is orally active, may be less effective than desferrioxamine, but is associated with improved compliance.

The pattern of distribution of iron varies between patients with iron overload due to primary haemochromatosis and those with transfusion-related iron overload. In primary haemochromatosis, increased amounts of iron are absorbed and deposited mainly in hepatocytes and the parenchymal cells of other organs. Increased iron deposition in reticuloendothelial cells, an important site of iron storage in normal individuals, usually does not occur in this disease until iron overload is far advanced. In contrast, transfusional iron overload is usually characterised by excessive accumulation of haemosiderin in the reticuloendothelial system first. Thus, in patients with transfusional iron overload, most hepatic iron is found in the Kupffer or phagocytic cells in the liver rather than the hepatic parenchymal cells. Significant involvement of parenchymal cells in the liver and other organs, leading to tissue damage, may occur in advanced cases. As iron overload in thalassaemia major is attributable not only to transfusion but also to increased intestinal iron absorption, iron can be deposited in both the hepatic parenchymal cells and the reticuloendothelial cells.

Regardless of whether iron overload is due to primary haemochromatosis or secondary to repeated blood transfusions, excess iron can accumulate in nearly all tissues, and the pattern of organ injury is the same. Most morbidity results from deposition in the liver, endocrine organs, heart, pancreas, and joints. Iron cardiomyopathy is of particular concern, and remains the leading cause of death for patients with thalassaemia major⁴. Whereas excess cardiac iron (which results in cardiac dysfunction) is the leading cause of death for patients with transfusional iron overload, patients with non-transfusional iron overload more commonly die of complications of iron overload in the liver.

The prognosis for patients with iron overload is influenced by many factors, including the age at which iron loading begins, the rate and route of iron loading, the distribution of iron deposition between macrophage and parenchymal sites, the amount and duration of exposure to circulating nontransferrin-bound iron, ascorbate status, and coexisting disorders, especially alcoholism and viral hepatitis³.

The characterisation of iron stores is, therefore, important to prevent and treat iron overload in these patients.

Existing procedures and tests

Quantitative studies of total iron stored in a patient at risk of iron overload have been limited by the lack of a reliable method for determining the total amount of iron in the body.

Total body iron stores can be measured by quantitative phlebotomy, but this approach cannot be used in transfusion-dependent patients with iron overload. It is generally acceptable only if the procedure provides therapeutic benefit³.

Several serum markers have been used to follow trends in a patient's iron status over time. These include serum ferritin, serum iron, and nontransferrin-bound iron, as well as total iron binding capacity and transferrin saturation⁴.

Trends in serum ferritin are considered a reasonable surrogate marker but results of tests to determine serum ferritin concentration can be confounded by the presence of infection, inflammation, malignancy, liver disease, ascorbate deficiency and other factors^{2,5}. Attempts to correlate serum ferritin with HIC have failed to demonstrate a linear relationship between the two parameters and discrepancies have frequently been observed⁶. Ferritin measurements are also poorly correlated with cardiac iron stores².

The correlation between serum ferritin concentration and individual HIC has been reported to be poor for patients with haemochromatosis ($r=0.63$) and for patients with thalassaemia major ($r=0.57$)⁷.

Nontransferrin-bound iron appears in the blood when transferrin is highly saturated, so its presence can be predicted by transferrin saturation values. Quantification of transferrin saturation is readily available; however, interlaboratory assay variability, rapid physiologic modification by inflammation, and nonlinearity with respect to total body iron levels limit the practical usefulness of this measure⁴.

HIC estimated through chemical assay of a biopsy sample of the liver has also been used as a surrogate for assessing total body iron stores^{8,2}. It is not surprising that liver iron levels reasonably reflect total body iron stores because the dominant iron storage organ is the liver, accounting for more than 70% of somatic iron stores^{2,4}. The standard technique for obtaining a liver biopsy specimen for histological evaluation is percutaneous needle biopsy. The Advisory Panel advised that biopsy is usually performed guided by ultrasound. The biopsy sample can also be used to detect fibrosis and cirrhosis, which have important prognostic implications for risk of hepatocellular carcinoma and survival.

It is notable that HIC correlates poorly with iron concentration in cardiac tissue because the mechanisms of iron uptake and clearance differ between organs⁴. In particular, iron is deposited and removed more quickly from the liver than from cardiac tissue, creating hysteresis between measured iron levels in these tissues. Many patients, particularly adolescents, can have high liver iron without detectable cardiac iron. If this situation exists long-term, cardiac iron begins to accumulate, even in the absence of additional hepatic iron loading. Conversely, intensive chelation can clear iron from the liver fivefold more quickly than the heart. Therefore, a patient may have high cardiac iron despite a lower total body iron burden following chelation therapy. Thus, HIC should not be used

as a surrogate to determine risk of cardiac complications for patients at risk of iron overload but should be used purely for assessment of the hepatic iron load⁹.

Assessment of iron concentration in the liver by needle biopsy is associated with other problems. There can be sampling error because the size of the biopsy is small relative to the size of the complete liver, and there can be variation in HIC from site to site within a liver, particularly in cirrhotic and fibrotic livers. There is also a decrease in precision as the overall iron load increases¹⁰. Secondly, needle biopsy of the liver is an unpleasant procedure for the patient and carries some degree of risk of adverse events (e.g., haemorrhage, infection, pain and, rarely, death). In paediatric, anxious or psychotic patients, administration of a sedative or even a general anaesthetic may be considered to facilitate the biopsy procedure. The unpleasantness associated with the procedure and the risk of adverse events limit the frequency with which HIC measurements by needle biopsy of the liver are made in practice.

R2-MRI data analysis is being assessed because it is potentially a non-invasive means to estimate iron concentration in the liver of individuals with or at risk of systemic iron overload.

Other potentially relevant technologies

There are several other technologies that could be relevant to MSAC's considerations because they have the potential to assess the extent of iron loading in various tissues. None of these technologies is currently included on the MBS.

- Other approaches to assessing HIC derived using data generated by MRI

The patented FerriScan® R2-MRI analysis system for estimating HIC incorporates a specific protocol for measurement of R2 and incorporates a specific calibration curve to estimate HIC from R2. It is currently the only R2-MRI data analysis package that has been approved by the TGA.

Several other MRI-based methods for assessing HIC have been reported in the literature over the past two decades. They generally fall into four main categories:

- signal intensity ratio methods based on T2 contrast
- signal intensity ratio methods based on T2* contrast
- relaxometry methods based on T2/R2 measurement
- relaxometry methods based on T2*/R2* measurement

Methods other than those used by the FerriScan® system for measuring T2/R2 have been used and reported in the literature. Assessment of T2*/R2* MRI data has been used to estimate concentration of iron in both hepatic and cardiac tissue. T2*/R2* methods are significantly faster and easier than T2/R2 methods. T2*/R2* information for multiple slices can be captured in a single breath-hold. However T2*/R2* measurements are vulnerable to distortions in the magnetic field produced by boundaries between materials having different magnetic susceptibility (e.g., in the presence of air-tissue interfaces [e.g., where there is excessive bowel gas] or in the presence of metal implants). T2/R2 imaging is more robust to susceptibility artifacts but images take longer to acquire than with T2*/R2* imaging. For example, the FerriScan® technique requires five minutes per set of echo times and 25 minutes

per examination. Therefore, such examinations must be performed with the patient free-breathing but respiratory motion disrupts the image quality.

Analysis of T2* has the potential to become the standard for measuring cardiac iron levels. MRI remains the only non-invasive modality in clinical use with the ability to detect the extent of iron deposition in cardiac tissue.

Summaries of a selection of studies reported in the literature comparing assessment of iron stores using MRI relaxometry data with results of biopsies are presented for information. In addition, a selection of studies comparing results of iron stores using MRI relaxometry data with results of clinical assessments are presented.

- Mavrogeni et al. (2005)¹¹, report the results of a study comparing assessment of cardiac iron deposition by T2-MRI data analysis with results from cardiac biopsy in 25 patients with beta-thalassaemia. Seven of the 25 patients had heart biopsy indicative of low iron deposition (Group L) and the remaining 18 patients had heart biopsies indicative of high iron deposition (Group H). T2 relaxation time of the heart was lower in Group H compared with Group L (31.5 ± 3.9 (range: 28–40) ms vs. 35.7 ± 3.7 (range: 29–40) ms, $p = 0.026$). The T2 relaxation time of the heart was in agreement with heart biopsy in 86% of the patients in Group L and in 78% of the patients in Group H (overall agreement 80%). A receiver operating characteristic curve (ROC) analysis confirmed that a T2 relaxation time of 32 ms had the highest discriminating ability for the corresponding biopsy outcome. The authors conclude that heart T2 relaxation time appears to agree with cardiac biopsy, both in high and low iron deposition, and may become a useful non-invasive index for patients with beta-thalassemia.
- Chandarana et al. (2009)¹², report the results of a study comparing T2* assessments with assessment of HIC by assay of material from liver biopsy or liver transplantation. Hepatic T2* values were compared between patients stratified by hepatic iron grade and were correlated with histopathologic iron grade. Receiver operating characteristics analysis was performed to assess the accuracy of images obtained with the hepatic T2*-weighted sequence in the diagnosis of iron deposition. Patients with iron deposition had shorter hepatic T2* values than did patients without iron deposition (mean T2*, 17.7 vs 32.3 ms with pooled data from both observers; $p < 0.0001$). Patients with iron grade 3 or greater had shorter T2* values than those with iron grade 2 or less (10.1 vs 20.8 ms; $p < 0.0001$). There was a strong negative correlation between hepatic T2* and histopathologic iron grade ($r = -0.849$; $p < 0.0001$). For the prediction of iron grades 1 or greater and 3 or greater, area under the curve, sensitivity, and specificity were 0.968-0.982, 90.5-100%, and 100-97.3% at T2* cutoffs of less than 24 and less than 14 ms, respectively. The authors conclude that hepatic iron overload in patients with liver disease can be assessed rapidly and accurately with MRI performed with a T2*-weighted sequence.
- Hanking et al. (2009)¹³, report the results of a comparison of assessment of HIC by R2* with results of assessment of HIC by liver biopsy within 30 days. Forty three patients (sickle cell anemia, $n = 32$; beta-thalassemia major, $n = 6$; and bone marrow failure, $n = 5$) were analysed. Regions of interest were drawn and analysed by three independent reviewers with excellent agreement of their measurements (intraclass correlation coefficient = 0.98). Ferritin and R2*-MRI were weakly but significantly associated (range of correlation coefficients among

the three reviewers, 0.41-0.48; all $P < .01$). $R2^*$ -MRI was strongly associated with HIC for all three reviewers (correlation coefficients, 0.96-0.98; all $P < .001$). The authors claim that the high correlation confirms prior reports of the accuracy of $R2^*$ -MRI measurements as an indicator of HIC and suggests its clinical utility for predicting HIC using $R2^*$ -MRI.

- Anderson et al. (2001)¹⁴, report the results of a study comparing HIC by liver biopsy with results for $T2^*$ -MRI data analysis in 30 patients with beta-thalassaemia. In addition, assessment of myocardial iron measured by this $T2^*$ -MRI data analysis was compared with ventricular function in 106 patients with thalassaemia major. A significant, curvilinear, inverse correlation between iron concentration by biopsy and liver $T2^*$ ($r=0.93$, $P<0.0001$) was reported. Inter-study cardiac reproducibility was 5.0%. As myocardial iron increased, there was a progressive decline in ejection fraction ($r=0.61$, $P<0.001$). All patients with ventricular dysfunction had a myocardial $T2^*$ of <20 ms. There was no significant correlation between myocardial $T2^*$ and the conventional parameters of iron status, serum ferritin and liver iron. Multivariate analysis of clinical parameters to predict the requirement for cardiac medication identified myocardial $T2^*$ as the most significant variable (odds ratio 0.79, $P<0.002$). The authors conclude that myocardial iron deposition can be reproducibly quantified using myocardial $T2^*$ and this is the most significant variable for predicting the need for ventricular dysfunction treatment. Myocardial iron content cannot be predicted from serum ferritin or liver iron, and conventional assessments of cardiac function can only detect those with advanced disease. It is claimed that early intensification of iron chelation therapy, guided by this technique, should reduce mortality from this reversible cardiomyopathy.
- Kirk et al. (2009)¹⁵, report the results of a study determining the predictive value of cardiac $T2^*$ magnetic resonance for heart failure and arrhythmia in thalassaemia major. Cardiac and liver $T2^*$ magnetic resonance and serum ferritin were assessed in 652 thalassaemia major patients. The relative risk for heart failure with cardiac $T2^*$ values <10 ms (compared with >10 ms) was 160 (95% confidence interval, 39 to 653). Heart failure occurred in 47% of patients within one year of a cardiac $T2^*$ <6 ms with a relative risk of 270 (95% confidence interval, 64 to 1129). The area under the receiver-operating characteristic curve for predicting heart failure was significantly greater for cardiac $T2^*$ (0.948) than for liver $T2^*$ (0.589; $P<0.001$) or serum ferritin (0.629; $P<0.001$). Cardiac $T2^*$ was <10 ms in 98% of scans of patients who developed heart failure. The relative risk for arrhythmia with cardiac $T2^*$ values <20 ms (compared with >20 ms) was 4.6 (95% confidence interval, 2.66 to 7.95). Arrhythmia occurred in 14% of patients within one year of a cardiac $T2^*$ of <6 ms. The area under the receiver-operating characteristic curve for predicting arrhythmia was significantly greater for cardiac $T2^*$ (0.747) than for liver $T2^*$ (0.514; $P<0.001$) or serum ferritin (0.518; $P<0.001$). The cardiac $T2^*$ was <20 ms in 83% of scans of patients who developed arrhythmia. The authors conclude that cardiac $T2^*$ magnetic resonance identifies patients at high risk of heart failure and arrhythmia from myocardial siderosis in thalassaemia major and is superior to serum ferritin and liver iron. They claim that using cardiac $T2^*$ for the early identification and treatment of patients at risk is a logical means of reducing the high burden of cardiac mortality in myocardial siderosis.

- Superconducting quantum interference device (SQUID)

SQUID is an imaging modality that uses a very low-power magnetic field with sensitive detectors that measure the interference of iron within the field. A measurement is performed by lowering the patient into a known, constant magnetic field and then detecting the change in magnetic flux versus the change in a water reference medium. The sensor requires a cryogenic environment, since it must be superconducting to operate. Although linear correlations have been demonstrated between SQUID measurements and iron levels from liver biopsy, SQUID is still considered an investigational technology. Although SQUID directly measures the magnetic susceptibility of ferritin and haemosiderin, it does not, at present, have sufficient spatial or temporal resolution to evaluate myocardial iron. The use of SQUID is currently limited because there are only four facilities worldwide that have a SQUID machine available for the measurement of iron levels.¹⁶

Marketing status of device / technology

The R2-MRI Analysis System (FerriScan®) has been registered by the TGA for the analysis of liver R2 and liver iron concentrations in individuals with, or at risk of, systemic iron overload where:

- a definitive diagnosis of iron overload is required; or
- to monitor the liver iron burden as part of ongoing clinical management.

Current reimbursement arrangements

R2-MRI analysis technology involves the use of two components:

- (i) acquisition of MRI data;
- (ii) analysis of data from the MRI to estimate iron concentration in the liver. No items currently included on the MBS specifically cover either of these two components.

Relevant existing procedures and tests that are included on the MBS include: standard needle biopsy, assessment of serum ferritin levels, either singly or as part of iron studies. Table 10 provides a list of relevant MBS items.

Table 10: Relevant MBS items

Item	Description and fee [^]
<u>Venesection</u>	
13757	Therapeutic venesection for the management of haemochromatosis, polycythemia vera or porphyria cutanea tarda Fee: \$67.40
<u>Blood tests</u>	
66593	Ferritin – quantitation, except if requested as part of iron studies Fee: \$18.10
66569	Iron studies, consisting of quantitation of: (a) serum iron; and (b) transferrin or iron binding capacity; and (c) ferritin Fee: \$32.75
<u>Items related to assessment of iron in tissue sample collected by biopsy</u>	
20702	Initiation of management of anaesthesia for percutaneous liver biopsy (4 basic units) Fee: \$73.20
55036	ABDOMEN, ultrasound scan of, including scan of urinary tract when undertaken but not being a service associated with the service described in item 55600 or item 55603, where: (a) the patient is referred by a medical practitioner for ultrasonic examination not being a service associated with a service to which an item in Subgroups 2 or 3 of this Group applies; (b) the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member; and (c) the service is not performed with item 55038, 55044 or 55731 on the same patient within 24 hours (R) Fee: \$111.30
30409	Liver biopsy, percutaneous (Anaes.) Fee: \$161.20
66831	Quantitation of copper or iron in liver tissue biopsy Fee: \$31.15

[^] Source: August 2009 Medicare Benefits Schedule

Approach to assessment

Objective

To carry out a structured assessment of the following technology: assessment of HIC by R2-MRI data analysis, based on a consideration of:

- the clinical need for the technology
- the clinical effectiveness of the technology
- the safety of the technology
- economic considerations.

Clinical decision pathway

The Advisory Panel advised that the populations who have the greatest capacity to benefit from a non-invasive accurate means of assessing iron load in the liver include:

1. the population at risk of liver disease due to non-transfusional iron overload (e.g., patients with primary haemochromatosis) defined by either:
 - (i) serum ferritin levels >1000ng/mL, or
 - (ii) serum ferritin levels >500ng/mL and abnormal liver function.
2. the population with or at risk of transfusional iron overload, which primarily consists of:
 - (i) children with severe haemoglobinopathies (such as thalassaemia major) who have received >50 units of blood
 - (ii) adults with severe haemoglobinopathies (such as thalassaemia major)
 - (iii) adults with myelodysplastic disorders with serum ferritin levels >1000ng/mL.

The population at risk of non-transfusional iron overload is distinguished from the population with or at risk of transfusional iron overload because the management of the former group of patients differs from that of the latter. Patients with non-transfusional iron overload are typically managed by serial phlebotomy whereas patients with transfusional iron overload are managed by administration of chelating agents.

Three subgroups of the population with or at risk of transfusional iron overload are distinguished from each other for the following reasons:

- Patients with severe haemoglobinopathies are differentiated from patients with myelodysplastic conditions on the grounds that patients with severe haemoglobinopathies are typically diagnosed with the condition early in life and have decades in which to develop morbidities related to iron overload, whereas patients tend to be diagnosed with myelodysplastic conditions late in life.
- Paediatric patients with severe haemoglobinopathies are distinguished from adult patients on the grounds that analysis of R2-MRI data to estimate HIC is more likely to replace liver biopsy in paediatric patients than in adult patients.

Typical management algorithms for the main populations (those at risk of liver disease from non-transfusional iron overload and those with or at risk of transfusional iron overload) are presented in Figure 7 and Figure 8. For each population, the management algorithm in a scenario where R2-MRI data analysis is not available (the current scenario) and the management algorithm where R2-MRI data analysis is available (the proposed scenario) is presented.

- For patients with non-transfusional iron overload, R2-MRI is positioned as a screening tool to identify patients who should be followed up with liver biopsy to determine the presence of liver disease (e.g., cirrhosis). The Advisory Panel advised that patients who are confirmed as having liver disease (e.g., cirrhosis) are then managed by regular liver biopsy to monitor for progression of liver disease to hepatocellular carcinoma. Patients who are demonstrated to not have liver disease are initiated on treatment with serial quantitative phlebotomy to prevent development of liver disease. Theoretically, patients newly diagnosed with haemochromatosis should require only a single assessment of R2-MRI to determine their HIC. However, the Advisory Panel advised that the use of R2-MRI data analysis, if included on the MBS, should be permitted to be used once every three years to allow for management of patients who are diagnosed with haemochromatosis but who are temporarily lost to follow-up or who are non-compliant with the recommended venesection schedule.
- For patients with or at risk of transfusional iron overload, R2-MRI data analysis is positioned as a tool to both diagnose iron overload in the liver and monitor change in iron content of the liver over time. It is positioned as a substitute for liver biopsy. The Advisory Panel advised that use of R2-MRI data analysis, if included on the MBS, should be limited to once annually for patients at risk of transfusional iron overload.

Figure 7: Management algorithm for patients at risk of liver disease due to non-transfusional iron overload

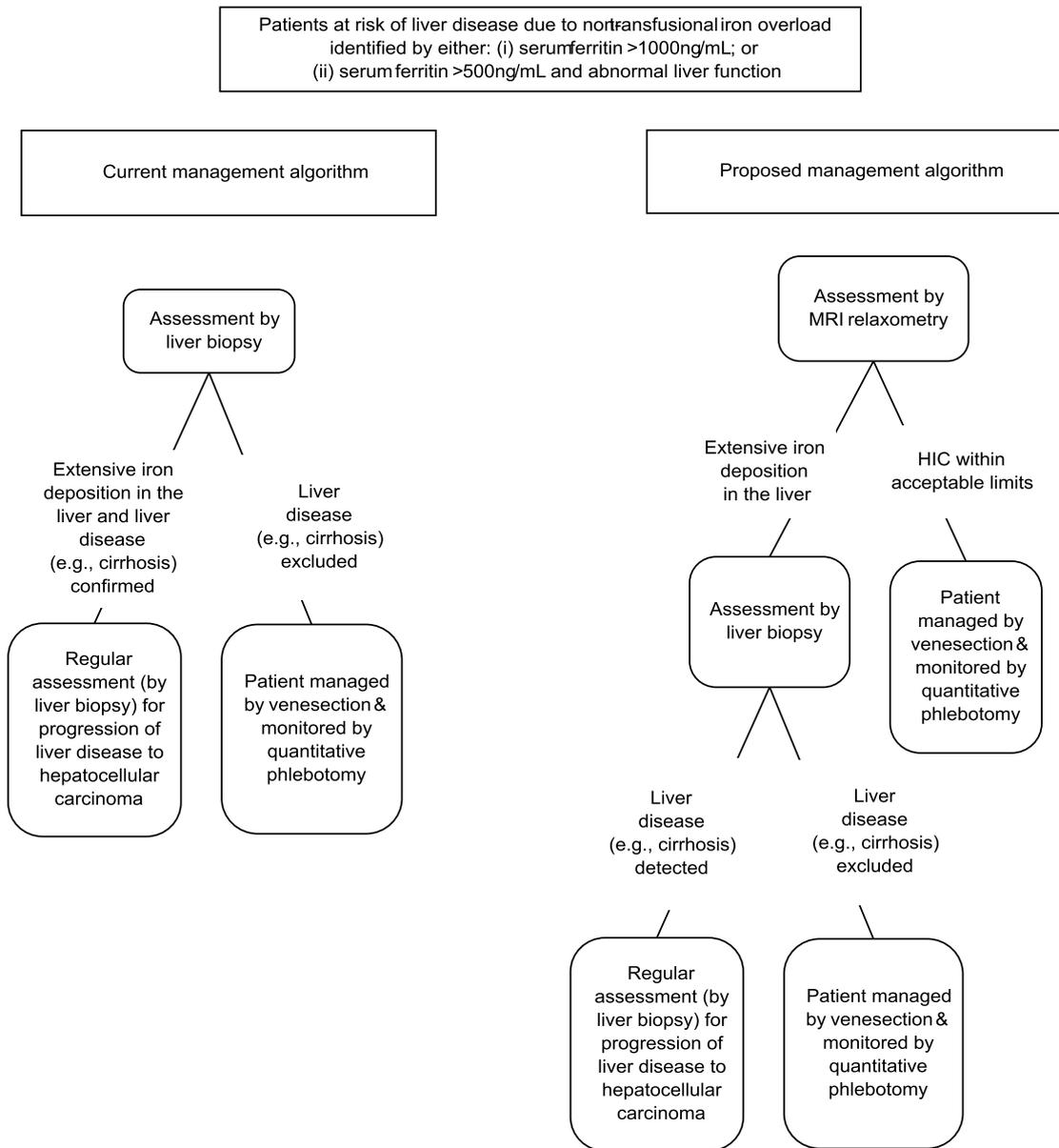
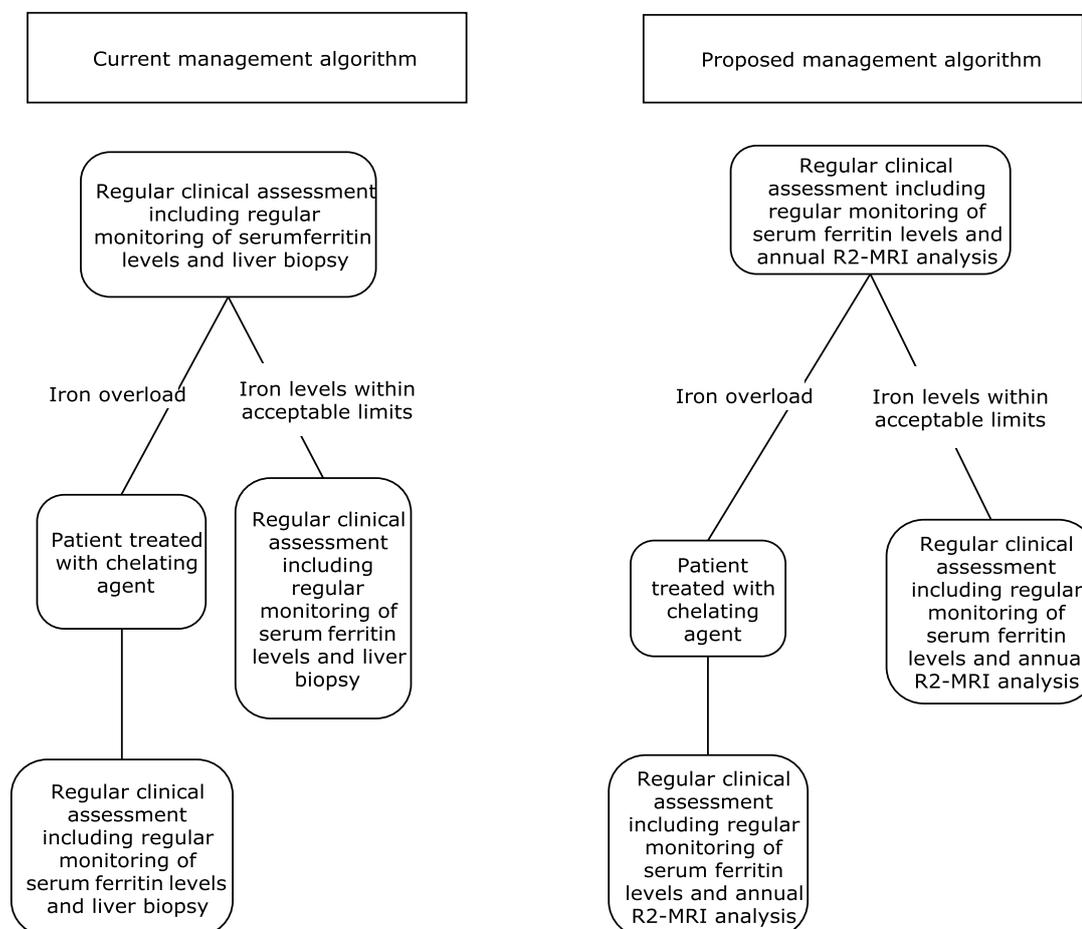


Figure 8: Management algorithm for patients with or at risk of transfusional iron overload

Population with, or at risk of, transfusional iron overload, which primarily consists of:

- children with severe haemoglobinopathies (such as thalassaemia major) who have received >50 units of blood
- adults with severe haemoglobinopathies (such as thalassaemia major)
- adults with myelodysplastic disorders with serum ferritin levels >1000ng/L.



Comparator

The appropriate comparator for an assessment of a technology by MSAC is the test or procedure most likely to be replaced in practice if the technology under consideration were to be made available.

For all patients, R2-MRI data analysis is unlikely to affect the use of indirect methods used to monitor iron levels in the liver (e.g., serum ferritin). Indirect methods are the primary methods for monitoring changes in iron load over short periods (e.g., month to month).

It was considered that, for patients with primary haemochromatosis, assessment of HIC by analysis of R2 data from MRI scans will substitute for assessment of liver iron by chemical assay of a liver biopsy sample. It is proposed that R2-MRI data analysis would substitute for liver biopsy for patients newly diagnosed with haemochromatosis.

Currently, liver biopsy is indicated for all patients diagnosed with haemochromatosis to:

- (i) assess the extent of iron overload in the liver; and
- (ii) detect liver disease. Patients with haemochromatosis who have iron overload in the liver are at high risk of liver disease (e.g., cirrhosis).

The presence of liver disease has important prognostic implications for risk of hepatocellular carcinoma and survival. It is proposed that, if R2-MRI data analysis is on the MBS, patients would have HIC assessed by R2-MRI, and then only patients diagnosed with iron overload in the liver would be referred for liver biopsy to test for liver disease.

Patients with primary haemochromatosis who are treated with venesection can have total body iron stores measured by quantitative phlebotomy. Analysis of R2 data from MRI scans will not replace phlebotomy because phlebotomy is primarily performed to provide patients with a therapeutic benefit.

For patients with transfusion-related iron overload (i.e., patients with severe haemoglobinopathies and patients with myelodysplastic conditions), assessment of serum ferritin is the primary method for monitoring changes in iron load over short periods. However, it is widely accepted that liver biopsy is, currently, the most reliable method for assessing extent of iron overload in such patients. Although assessment of HIC by liver biopsy is desirable and indicated for such patients, the extent to which it is used in practice varies among centres that manage patients with transfusion-related iron overload.

The primary comparator assumed to be relevant in this assessment of R2-MRI data analysis technology is chemical assay of a liver biopsy sample. However, it is acknowledged that for some patients (e.g., those for whom liver biopsy is indicated but not undertaken) the comparator is no assessment of HIC.

The reference standard

The MSAC guidelines on assessment of diagnostic tests (2005) state: ‘Any technology or procedure that is used to confirm, exclude or classify disease is referred to as a diagnostic test in this document. Classification of disease is undertaken to grade the severity, size, shape, location or other clinically meaningful subgroups. The rationale for performing a diagnostic test is to guide treatment, indicate prognosis, monitor disease progress or evaluate the effectiveness of current treatment (Deeks 2001; Sackett et al. 1999).’ Because the technology was used to attribute an iron level to a patient and this iron level (in conjunction with serial measurements) was used to guide treatment, the technology was considered to satisfy MSAC’s definition of a diagnostic intervention. On this basis, the intervention has been assessed in accordance with the MSAC guidelines applying to diagnostic interventions.

The accuracy of a diagnostic technology is typically assessed by comparing the results generated by that technology with the results generated by an accepted reference standard.

A true reference standard that provides an absolute measure of HIC in a living patient’s liver is not available. Of the available methods for assessing HIC, chemical analysis of a specimen from the liver collected by needle biopsy, is considered the best. However, as discussed in the section titled ‘Existing procedures and tests’, the estimate of HIC

generated by this method is subject to sampling error. This is mainly due to the small size of the biopsy relative to the size of the complete liver. There can be variation in HIC from site to site within a liver, particularly in cirrhotic and fibrotic livers. Additionally, biopsy of the liver is an unpleasant procedure for the patient and carries some degree of risk of adverse events.

For the purposes of this assessment, the accuracy of estimation of HIC using R2-MRI data analysis is compared with results of chemical analysis of a liver specimen collected by needle biopsy. However, consideration has been given to the potential for this technology to overcome the limitations of HIC estimated by chemical analysis of a specimen from the liver collected by needle biopsy.

Research questions

The research question addressed by this assessment is:

Will the use of R2-MRI data analysis to estimate iron concentration in the liver of individuals with or suspected of systemic iron overload result in an improvement in quality-adjusted survival compared with current assessment of hepatic iron concentration that excludes the use of such a technology?

The following populations who may be diagnosed with or who may be suspected of systemic iron overload are specifically considered:

- *Patients at risk of liver disease due to non-transfusional iron overload, e.g., patients with haemochromatosis and patients with thalassaemia intermedia.* It is assumed that only patients at risk of liver disease, defined by serum ferritin levels >1000 ng/mL and elevated alanine aminotransferase (ALT) levels, should be considered suitable for assessment with this technology.
- *Children with severe haemoglobinopathies who are at risk of iron overload due to receipt of multiple blood transfusions (>50 units of blood) to manage their anaemia.* The majority of patients in this category will be patients with thalassaemia major but the classification includes patients with rarer conditions such as Diamond Blackfan anaemia. Patients are assumed not to be required to reach any specific threshold level for serum ferritin in order to be suitable for assessment with this technology.
- *Adults with severe haemoglobinopathies who are at risk of iron overload due to a need for multiple transfusions to treat the anaemia.* Patients are assumed not to be required to reach any specific threshold level for serum ferritin in order to be suitable for assessment with this technology.
- *Adults with myelodysplastic conditions who are at risk of iron overload due to a need for multiple transfusions to manage the condition.* It is assumed that only patients with serum ferritin levels >1000 ng/mL should be considered suitable for assessment with this technology.

The preliminary searches of the literature found no reports of studies that investigated the implications of including R2-MRI data analysis (for the purpose of estimating HIC) in protocols for managing patients at risk of iron overload for final patient outcomes (e.g., survival, quality-adjusted survival). The research question was therefore broken into the following parts:

- What is the accuracy of R2-MRI in *diagnosing* liver iron overload and in *monitoring* iron load in the liver?

The use of R2-MRI is differentiated according to whether the HIC is required for diagnosis or for monitoring. In the case of a diagnostic setting, the objective of the use of the technology is to determine whether some *absolute* threshold level of iron has been reached in the liver, whereas in the case of the monitoring setting, it is the direction and magnitude of *change* in iron concentration over time that is important.

- In response to information provided by R2-MRI analysis, what changes will ensue in the treatment decisions made by clinicians?
- As a result of more appropriate treatment decisions, will patients experience improved health outcomes?

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews to inform the assessment of R2-MRI data analysis as a means of estimating iron concentration in the livers of patients with or suspected of systemic iron overload. Table 11 lists the electronic databases searched and the periods covered by the searches.

Table 11: Electronic databases searched

Database	Period covered
Ovid Medline	1950-24 June 2009
Embase	to 2 July 2009
Cochrane DSR, ACP Journal Club, DARE, CCTR, HTA and NHSEED	to 3 July 2009

The search terms used included: R2-MRI analysis, liver R2, spin density R2-MRI, R2 magnetic resonance imaging, St Pierre, FerriScan, liver MRI, spin density projection, relaxometry, liver iron, hepatic iron, iron overload.

The aim of this search strategy was to be as inclusive as possible of all studies that may have investigated the assessment of HIC using R2-MRI data analysis.

Selection criteria

Table 12 summarises the selection criteria applied in the electronic searches. The search of the literature was barely constrained to ensure that all studies that may have investigated the assessment of HIC using R2-MRI data analysis were located.

Table 12: Selection criteria for included studies

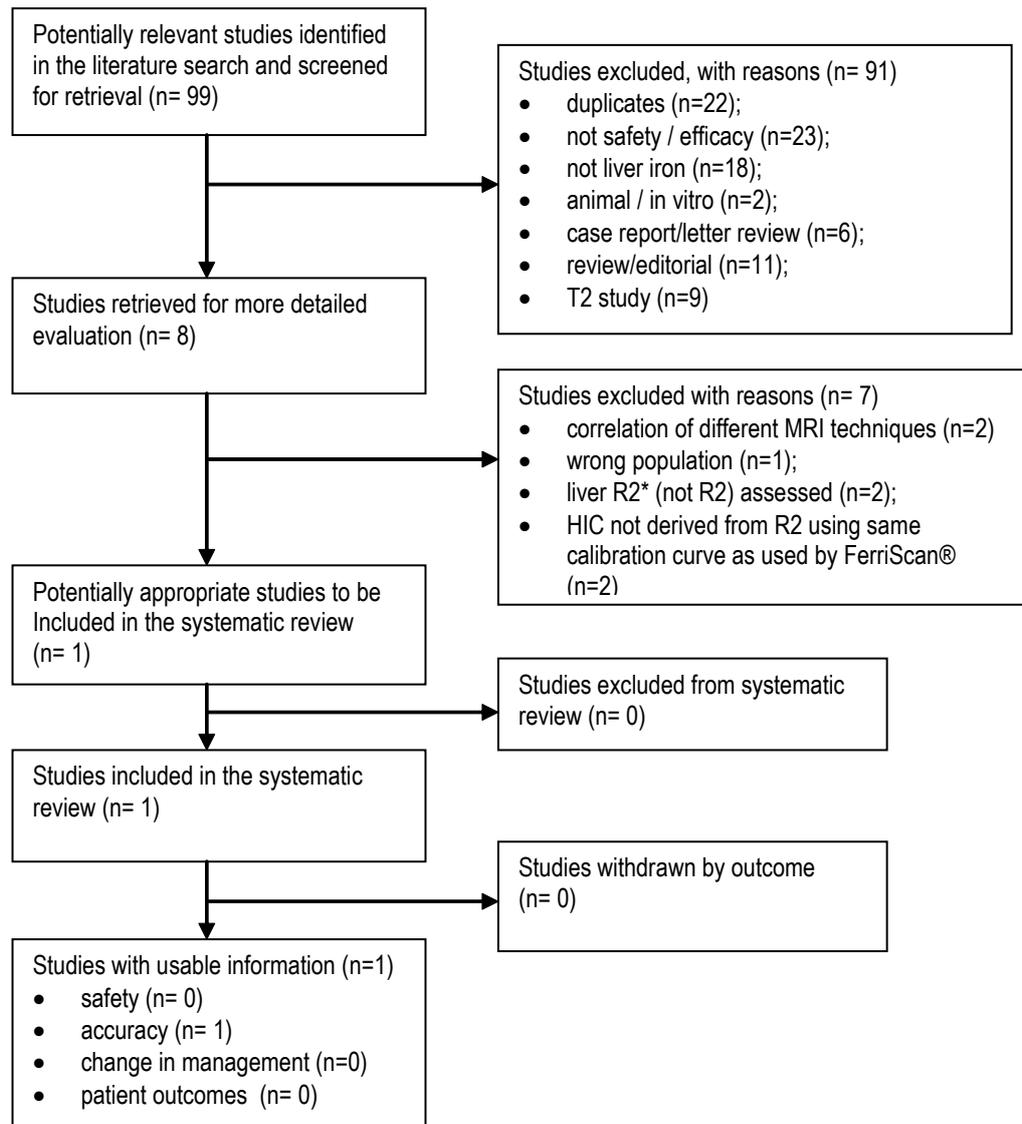
Research question: Will the use of R2-MRI data analysis to estimate iron concentration in the livers of individuals with or suspected of systemic iron overload result in an improvement in quality-adjusted survival compared with current assessment of hepatic iron concentration that excludes the use of such a technology?		
Selection criteria	Inclusion	Exclusion
Study design	All study designs	None
Population	Iron overload	Animal
Prior tests	Not specified	None
Intervention	R2 data analysis	None
Reference standard	Not specified	None
Comparator	Not specified	None
Outcomes	None specified	None
Publication type	None specified	None

Search results

The publications located by the electronic searches were then assessed to identify those reporting the results of studies that may have investigated the assessment of HIC using R2-MRI data analysis. Figure 9 summarises the process used to identify all studies assessing the efficacy or safety of R2-MRI data analysis for the quantification of iron in patients with or suspected of iron overload. Only studies examining the accuracy of R2-MRI analysis conducted in accordance with the protocol used by the patented FerriScan® R2-MRI analysis system were retrieved. FerriScan® incorporates a specific protocol for measurement of R2 and features a specific calibration curve to estimate HIC from R2. It is currently the only R2-MRI data analysis package that has been approved by the TGA.

Quorum Flowchart

Figure 9: Summary of the process used to identify studies assessing the efficacy or safety of R2-MRI data analysis for the quantification of iron in patients with or suspected of iron overload.



Adapted from Moher et al. (1999)

A linked search was undertaken because no studies were located that investigated the implications of including R2-MRI data analysis (for the purpose of estimating HIC) in protocols for managing patients at risk of iron overload for final patient outcomes (e.g., survival, quality-adjusted survival). Relevant publications are classified according to the question being addressed.

1) Is the test safe?

The literature search did not locate any reports that related to studies that addressed the safety of R2-MRI. Given that R2-MRI is a software program, it is unlikely that there will be any adverse events associated with its use. However, there may be safety

concerns with repeated use of magnetic resonance scanning and this is addressed in the “Is it safe?” section on p. 31 of this report.

2) Is the test accurate?

The literature search located the report of a single study that directly addressed whether R2-MRI (where R2 assessments are transformed to estimates of HIC assuming the same calibration curve incorporated into the FerriScan® software) was accurate when compared with chemical assay of a liver biopsy sample:

- St Pierre TG, Clark PR, Chua-anusom W et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood* 2005; 105:855-861.

3) Does the test change patient management?

The provision of more accurate estimates of HIC has the potential to change how a patient is managed, particularly the details of the administration of chelating agents (choice of agent, mode of administration, dose, frequency, etc.).

The literature search did not locate any reports of studies that addressed this question. However, the application to MSAC requesting subsidy of R2-MRI data analysis did include one unpublished study which is discussed in this assessment.

4) Does the treatment change health outcomes?

Phlebotomy, in conjunction with surveillance for hepatocellular carcinoma in patients with cirrhosis of the liver at diagnosis, is the accepted treatment for management of patients with hereditary haemochromatosis. Chelation therapy is the accepted treatment for treating transfusional iron overload. The use of such interventions to manage or prevent iron overload is well established in these conditions. Therapeutic venesection for the management of haemochromatosis is reimbursed under the MBS (MBS Item 13757), and chelating agents (desferrioxamine, deferiprone and deferasirox) are reimbursed under the Pharmaceutical Benefits Scheme (PBS). This assessment assumes that the effectiveness of these therapies is not in dispute and that a change in management to better guide therapy will be associated with improved patient outcomes.

Data extraction and analysis

Data were extracted using standardised extraction forms which include key parameters: study population, intervention, analyses and outcomes. Data extraction was performed by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion to gain consensus. Data were only reported if stated in the text, tables, graphs or figures of the article, or if they could be accurately extrapolated from the data presented.

Appraisal of the evidence

Appraisal of the evidence was conducted in three 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 to make 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) in their handbook, *How to use the evidence: assessment and application of scientific evidence*¹⁷.

These dimensions (summarised in Table 13) 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 the assessment of a particular intervention. Each of the last two requires expert clinical input as part of its determination.

Table 13: 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 <i>p</i> -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.

* See Table 14

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 that is addressed (Table 14).

Table 14: Designations of levels of evidence according to type of research question (see also table footnotes)¹⁸

Level	Intervention¹	Diagnostic accuracy²	Prognosis	Aetiology³	Screening Intervention
I⁴	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	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	A prospective cohort study ⁷	A prospective cohort study	A randomised controlled trial
III-1	A pseudo randomised controlled trial (i.e., alternate allocation or some other method)	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	All or none ⁸	All or none ⁸	A pseudo randomised controlled trial (i.e., alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomised, experimental trial⁹ ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study¹⁰ ▪ Interrupted time series without a parallel control group 	Diagnostic case-control study ⁶	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ¹¹	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Notes to Table 14:

- ¹ Definitions of these study designs are provided on pages 7-8 of the NHMRC handbook: *How to use the evidence: assessment and application of scientific evidence*¹⁷.
 - ² The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes^{19,20}.
 - ³ If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e., cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.
 - ⁴ A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, because different studies (and study designs) might contribute to each different outcome.
 - ⁵ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study²¹.
 - ⁶ Well-designed population-based case-control studies (e.g., population-based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease is compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease and conditions mimicking the disease are excluded, which can lead to exaggeration of sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice²².
 - ⁷ At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.
 - ⁸ All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series, which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus, and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.
 - ⁹ This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e., utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).
 - ¹⁰ Comparing single-arm studies i.e., case series from two studies. This would also include unadjusted indirect comparisons (i.e., utilise A vs B and B vs C, to determine A vs C, but where there is no statistical adjustment for B).
 - ¹¹ Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.
- Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.
- Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question (e.g., level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence).
- Source: Hierarchies adapted and modified from: NHMRC (1999)²³; Bandalier (1999)²⁴; Lijmer et al. (1999)²⁵; Phillips et al. (2001)²⁶.

Individual studies assessing diagnostic effectiveness were graded according to pre-specified quality and applicability criteria specified by the MSAC Guidelines¹⁹, as shown in Table 15.

Table 15: 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

The appraisal of intervention studies pertaining to treatment safety and effectiveness was undertaken using a checklist developed by the NHMRC²⁷. This checklist was used for trials and cohort studies. Uncontrolled before-and-after case series are a poorer level of evidence with which to assess effectiveness. The quality of this type of study design was assessed according to a checklist developed by the UK National Health Service (NHS) Centre for Reviews and Dissemination²⁸. Studies of diagnostic accuracy were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) quality assessment tool²¹.

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 chance¹⁷.

Size of effect

For intervention studies of R2-MRI data analysis it was important to assess if statistically significant differences between the comparators were also clinically important. The size of the effect needed to be determined, as well as if the 95% confidence interval included only clinically important effects.

Relevance of evidence

The outcomes measured in this report should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided¹⁷.

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 development²⁹. 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 – if the better quality studies had results of a similar magnitude and in the same direction (i.e., 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 (Table 16).

Table 16: Body of evidence assessment matrix

Body of evidence Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III study with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	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
Generalisability	population/s studied in body of evidence are the same as the target population	population/s studied in the body of evidence are similar to the target population	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	population/s studied in body of evidence different 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

Adapted from NHMRC document²⁹

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 consumer interests into account. Membership of the Advisory Panel is listed in Appendix A.

Results of clinical assessment

Is it safe?

As discussed in the section titled ‘Search results’, which summarises the results of the literature search, no reports relating to studies that specifically investigate the safety of R2-MRI analysis were found. R2-MRI data analysis is a software application that interprets data captured by MRI. Therefore, the safety of R2-MRI data analysis can be separated into:

- (i) the safety of the software application; and
- (ii) the safety of MRI scans—particularly, regular repeated MRI scans.

Analysis of R2-MRI data is conducted by a software program that has no direct interaction with the MRI scanner, patient, or environment. It would be reasonable to assume that there will be no adverse events associated with the use of the software. There may be safety concerns with the use of the MRI scan itself, particularly with repeated scans. The safety of regular MRI scans was assessed by a review of the literature. The references listed in Table 17 were retrieved and used to assess the safety of MRI, particularly repeated MRI scans.

Table 17: Literature consulted for review of the safety of MRI

Report	Study design and quality appraisal	Population	Adverse events
Hartwig et al., 2009 ³⁰ .	Review of the effects of non-ionising electromagnetic fields employed in MRI, relevant to patients' and workplace safety.	N/A	N/A
Formica & Silvestri, 2004 ³¹	Review of the bio-effects produced by MRI systems acting directly on the human body.	N/A	N/A
Keevil et al., 2005 ³²	Commentary.	N/A	N/A
De Wilde et al., 2007 ³³	Case series report. Summarises safety issues and risks associated with exposure to MRI.	Patients undergoing clinical MRI in the United Kingdom between January 1990 and November 2006.	163 user incidents and 58 vigilance reports were reported. Specific numbers for each incident type are not provided.
Independent Advisory Group on Non-ionising Radiation, Health Protection Agency, 2008 ³⁴	Case series report. Review produced by independent Advisory Group on Non-ionising Radiation summarising mechanisms for interaction, cellular, animal and human studies, trials, and case reports.	N/A	N/A
Dobson et al., 2009 ³⁵	Analytical observation. Evaluation of cellular effects via nano-magnetic actuation of endogenous iron oxides in human tissue.	N/A	N/A
Dempsey et al., 2002 ³⁶	Case series report. Review summarising the potential electromagnetic interactions within the MR imaging environment.	N/A	N/A
Schenck, 2000 ³⁷	Case series report. Review of issues associated with the exposure of patients to strong static magnetic fields during MRI.	N/A	N/A
Schenck, 2005 ³⁸	Review of proposed interactions of magnetic fields with human tissues.	N/A	N/A
Schenck et al., 1992 ³⁹	Cross sectional survey of 9 volunteers exposed to	33 adults	Sensory

Report	Study design and quality appraisal	Population	Adverse events
	whole-body scans at 4T and 1.5T and 24 patients exposed to 1.5T only.		sensations of vertigo, nausea, and metallic taste
New et al., 1983 ⁴⁰	Technical report. Evaluation of 21 aneurysm and hemostatic clips, and other biomedical implant materials for longitudinal forces and torques under nuclear magnetic resonance imaging.	N/A	N/A
Shellock & Crues, 1988 ⁴¹	Technical report. Evaluation of the ferromagnetic qualities of 36 different metallic biomedical implants for imaging safety with high-field-strength MR systems.	N/A	N/A
Shellock, 2002 ⁴²	Case report. Invited review evaluating MR safety and MR compatibility issues for a variety of implants and devices.	N/A	N/A

MRI does not involve ionising radiation, so it has been generally accepted as a ‘safe’ imaging modality as long as proper precautions are taken^{37,36}. MRI has the ability to change the positions of atoms but not to alter their structure, composition, and properties, as ionising radiation can do³⁰. However, a number of reviews have suggested that further evidence is required as the strength of magnetic fields used clinically is increased^{30,43,38,37}. There is no evidence of a cumulative effect on health due to repetitive exposure to magnetic fields^{38,37,39}.

The strong static magnetic fields used in MRI may pose a risk to patients. The main established hazard of MRI is the so-called ‘projectile’ or ‘missile effect’. As a result of the large gradient field, ferromagnetic objects that inadvertently enter the field are accelerated and become dangerous projectiles³⁶. Most reported cases of MRI-related injuries have been caused by misinformation related to the safety aspects of the magnetic resonance imaging environment. They include projectile and burn incidents, altered device function (e.g., cardiac pacemaker), and the presence of unknown foreign metal objects^{33,36}. Contraindications for MRI include the presence of internal cardiac pacemakers, implanted cardiac defibrillators, neurostimulators, bone growth stimulators, implanted drug infusion pumps, cochlear implants, ocular implants, metallic vascular access ports, and some aneurysm clips.

Adverse effects that have been associated with MRI include sensory effects such as nausea, vertigo, and metallic taste^{39,43}.

By comparison, liver biopsy is an invasive and painful procedure, and carries the risk of bleeding and infection, as well as damage to the liver or surrounding organs. However, fatal complications have rarely been reported^{44,45}. The safety of liver biopsy is enhanced by ultrasound guidance; a complication rate of 0.5% was reported in one large study⁴⁶.

Assessment of HIC by R2-MRI data analysis is likely to be associated with safety advantages when compared with assessment of HIC by liver biopsy.

Summary of comparative safety

No reports were located that related to studies that specifically investigated the safety of R2-MRI analysis. Therefore, no direct comparison of the safety of a scenario that includes the use of R2-MRI analysis versus a scenario that excludes such use is presented. In addition, no direct comparison of the safety of the use of R2-MRI analysis to determine HIC versus chemical assay of a sample from liver biopsy to determine HIC (the reference standard) is presented.

Analysis of R2-MRI data is conducted by a software program that has no direct interaction with the MRI scanner, patient or environment. It would be reasonable to assume that there are no adverse events associated with the use of the software. There may be safety concerns with the use of the MRI scan itself. MRI does not involve ionising radiation, so it has been generally accepted as a 'safe' imaging modality as long as proper precautions are taken.

By comparison, liver biopsy is an invasive and painful procedure, and carries the risk of bleeding and infection, and damage to the liver or surrounding organs. Fatal complications have rarely been reported. The safety of liver biopsy is enhanced by ultrasound guidance; a complication rate of 0.5% was reported in one large study.

Assessment of HIC by R2-MRI data analysis is likely to be associated with safety advantages when compared with assessment of HIC by liver biopsy.

Is it effective?

A search of the literature did not find any reports on the effectiveness (in terms of patient-relevant health outcomes such as survival and quality of life) of a management protocol involving R2-MRI analysis to estimate HIC compared with a protocol that did not involve the use of R2-MRI analysis for patients with, or at risk of, iron overload in the liver. Therefore, a series of questions linking various aspects of interest were considered:

Is it accurate?

Only one study was included in this assessment of the effectiveness of R2-MRI data analysis according to the criteria outlined in Table 18.

Table 18: Inclusion criteria for identification of studies relevant to an assessment of effectiveness of R2-MRI data analysis

Research Question	
Will management that involves the use of R2-MRI analysis to assess extent of iron load in the liver, compared with current management excluding such analysis, result in an improvement in quality-adjusted survival for:	
Selection criteria	Inclusion criteria
Population	None specified
Intervention	R2-MRI data analysis used to estimate HIC. Only studies examining the accuracy of R2-MRI analysis conducted in accordance with the protocol used by the patented FerriScan® R2-MRI analysis system (which incorporates a specific protocol for measurement of R2 and incorporates a specific calibration curve to estimate HIC from R2) were retrieved. It is currently the only R2-MRI data analysis package that has been approved by the TGA.
Comparator	None specified
Outcomes	None specified
Search period	No limits were applied in the searches conducted.
Language	Publications in any language will be included.

The study is:

St Pierre TG, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK, Pootrakul P, Robins E and Lindeman R. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood*, 15 January 2005; 105:855-861

Study design

The study had two purposes:

- (i) it derived a calibration curve to determine HIC from an average R2 value;
- (ii) it compared HIC as estimated by R2-MRI data analysis with HIC as estimated by chemical assay of a liver specimen obtained by needle biopsy.

This study undertook MRI on human subjects using five 1.5-T whole body imaging units (Siemens, MAGNETOM Vision Plus [n=4] and Siemens SONATA [n=1]). Phased array torso coils were used for signal detection. Axial images were acquired with a multislice single spin-echo (SSE) pulse sequence, with a pulse repetition time (TR) of 2500 ms, spin-echo times (TE) of 6, 9, 12, 15, and 18 ms, and slice thickness of 5 mm. A matrix

size of 256 was used with typical fields of view being between 350 and 400 mm (exact dimensions depending on subject size). Each spin-echo sequence was run with fixed gain settings determined by the TE=6 ms acquisition. Data was acquired in half-Fourier mode to reduce measurement time with one acquisition. No fat suppression was used. A 1000-mL bag of Hartmann's solution (compound sodium lactate) was imaged with both the phantoms and human subjects to provide an external long T2 reference for the correction of instrumental gain drift.

The technique used to calibrate the MRI scanners was consistent with the technique applied by the patented FerriScan® system (i.e., precision and accuracy of R2 measurements made using each MRI scanner was confirmed by the use of phantoms, which were solutions of MnCl₂ in varying concentrations).

The subjects who were included in the study were patients who were about to undergo liver needle biopsy for assessment of iron overload disorder or liver disease. The liver biopsy was to be used for both routine histologic examination and HIC measurement. The MRI scanning of these patients was scheduled as close as possible to the liver biopsy procedure (within a few days) or within one to two months for those whose liver biopsy results did not warrant clinical treatment for iron overload.

The chemical analysis for HIC measurement was conducted with atomic absorption spectrometry after acid digestion (four laboratories). All samples had dry weights more than 0.4 mg. Quality control studies for interlaboratory assay were first performed using standard reference liver material (National Bureau of Standards BL1577a) and aliquots from a homogenized specimen of iron-loaded liver tissue.

For the study, a lateral region of the right lobe of the liver, bounded by its surface and sagittal plane 35 mm medial to its most lateral surface point, was chosen for the R2 measurement, for the needle biopsy site, and to calculate a mean R2 value for purposes of generating a calibration curve relating R2 to HIC. To quantify the heterogeneity in R2 for a subject, the entire slice of the liver was used for calculation of the standard deviation (SD) of R2.

Patient characteristics

Subjects recruited in the study included:

- (i) a sample of patients with iron overload (23 patients with hereditary haemochromatosis, 9 patients with thalassaemia who had been treated with regular blood transfusion and chelation therapy, 41 patients with haemoglobin E/thalassaemia who had not received regular blood transfusions nor chelation therapy);
- (ii) a sample of patients with hepatitis who did not have iron overload (29 with hepatitis C, 2 with alcohol-induced hepatitis, 1 with drug-induced hepatitis).

Outcomes assessed and methods of analysis

Outcomes assessed for patients consisted primarily of:

- HIC as estimated by R2-MRI data analysis;
- HIC as estimated by chemical assay of a liver specimen obtained by needle biopsy.

The Spearman rank order test determined the nonparametric correlation between the R2 measurements and liver biopsy HIC. The calibration curve derived (as part of this study) to relate mean liver R2 values to biopsy HIC in the study was:

$$R2=6.88+26.06[Fe]^{0.701}-0.438[Fe]^{1.402}$$

The methods of Bland and Altman⁴⁷ were used to determine the 95% limits of agreement between R2-HIC measurements and biopsy HIC measurements. Sensitivity and specificity of the R2-HIC measurement to discrimination of biopsy HIC values above certain clinically important HIC thresholds were evaluated. Confidence limits for the sensitivity and specificity were obtained using the Wilson score method. Areas under ROC plots were evaluated at each of the clinically important HIC thresholds by calculating the true positive fraction and true negative fraction for detection of HICs above the clinically important threshold for each possible cut-off value of mean liver R2. Standard errors on the areas under the ROC plots were evaluated using the approximations of Hanley and McNeil⁴⁸.

A summary of the profile for the included study is in Table 19.

Table 19: Assessment of accuracy of assessment of HIC by R2-MRI data analysis

Study	Level and quality	Population	Interventions	Outcome
St Pierre et al. 2005	<p><i>Level of evidence:</i> III-2 (Diagnostic case-control study)</p> <p><i>Quality assessment:</i> C1 (direct comparison vs reference standard) P2 (the extent to which the population is representative of the population of interest is limited) Q2 (some potential for bias)</p>	<p>N=105</p> <p><i>Patients with iron overload (n=73):</i></p> <ul style="list-style-type: none"> • 23 patients with hereditary haemochromatosis • 9 patients with thalassaemia who had been treated with regular blood transfusion and chelation therapy • 41 patients with haemoglobin E /thalassaemia who had not received regular blood transfusions nor chelation therapy <p><i>Patients with hepatitis who did not have iron overload (n=32):</i></p> <ul style="list-style-type: none"> • 29 with hepatitis C • 2 with alcohol-induced hepatitis • 1 with drug-induced hepatitis 	<ul style="list-style-type: none"> • R2-MRI data analysis • Chemical assay of liver sample collected by needle biopsy 	<ul style="list-style-type: none"> • HIC as estimated by R2-MRI data analysis • HIC as estimated by chemical assay of a liver specimen obtained by needle biopsy <p>The methods of Bland and Altman were used to determine the 95% limits of agreement between R2-HIC measurements and biopsy HIC measurements. Sensitivity and specificity of the R2-HIC measurement to discrimination of biopsy HIC values above certain clinically important HIC thresholds were evaluated.</p>

Abbreviations: HH=Hereditary haemochromatosis

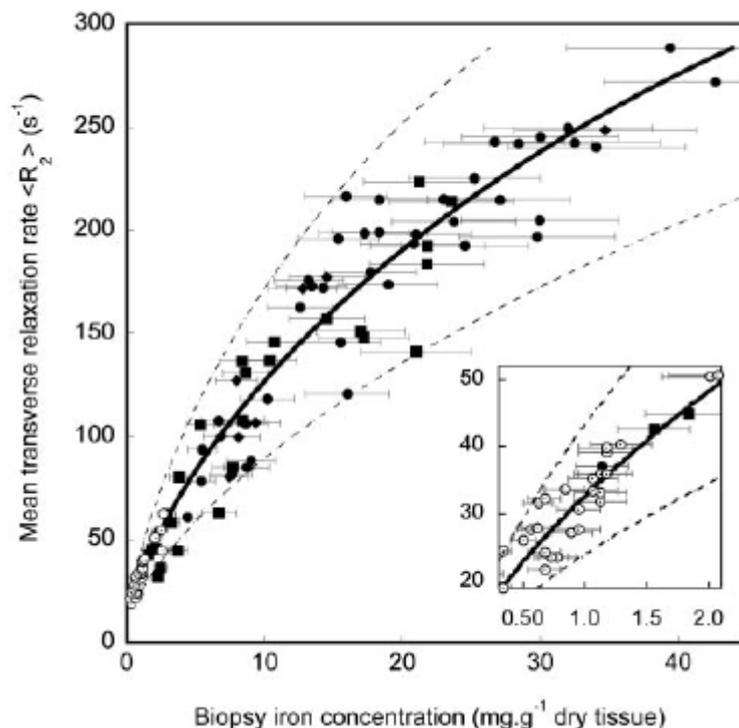
Results

Biopsy HIC values measured for the 105 human subjects ranged from 0.3 to 42.7 mg Fe/g dry liver tissue. Of the 105 biopsies used in this study, only 48 had the dry masses permanently recorded by the pathology laboratory. Of these, 17 (35%) had dry masses below 1 mg and 31 (65%) had dry masses more than 1 mg. As reported by Angelucci et al. (2000)⁴⁹, two conditions have to be met to obtain an accurate estimate of the HIC by chemical assay of a sample from liver biopsy. Firstly, no cirrhosis or focal

lesions should be present. In the absence of cirrhosis and focal lesions, iron is uniformly distributed within the liver, so that iron concentration in a sample is representative of that in the whole liver. Secondly, the liver sample should have a dry weight of at least 1.0 mg for reliable results.

The calibration curve shown in Figure 10 was derived from data from this study to estimate HIC from R2 values. The inset in Figure 10 is a magnification of the lower end of the curve, where results are those generated for subjects that were not iron loaded (i.e., for patients with hepatitis). The solid line is the calibration determined by curve fitting to the data. The error bars indicate the estimated 19% uncertainty around the HICs determined by biopsy. The uncertainty of 19% is based on studies of HIC heterogeneity in fibrosis-free liver. The dashed lines indicate the 95% limits of agreement between R2-LIC and biopsy LIC. Subject groups that are distinguished in this figure (and the symbols used in the figure for each group) are those with hepatitis (○), hereditary haemochromatosis (■), haemoglobin E/thalassaemia (●), and thalassaemia (◆). A highly significant correlation ($p=0.98$, $P<0.0001$) was found between biopsy HIC and liver R2 measurements for the region of interest (the right lobe of the liver) as determined by the Spearman rank order test for all subjects. St Pierre et al. note that there is a general increase in R2 variability throughout the liver with increasing biopsy HIC, which is evidenced by a broadening of the R2 distribution at higher biopsy HIC.

Figure 10: R2-HIC calibration curve



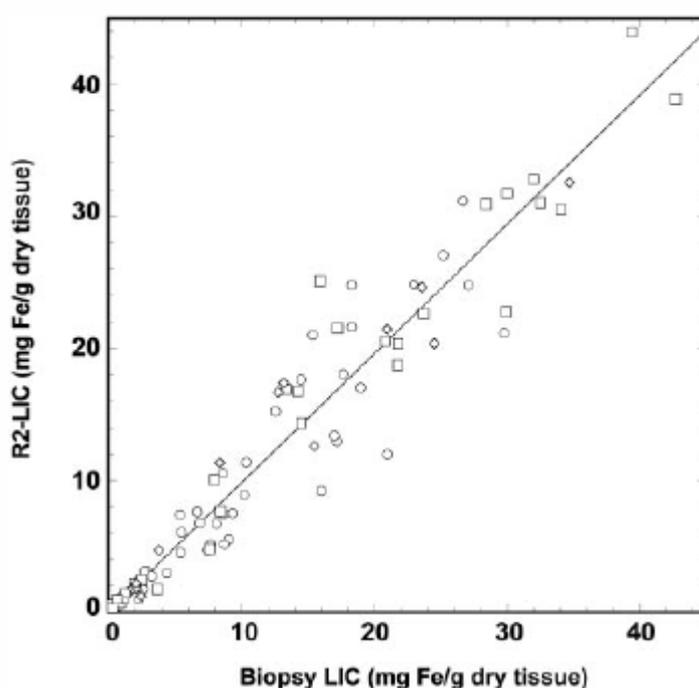
The sensitivities and specificities of the measured liver R2 values for the discrimination of biopsy HIC values above various clinically significant thresholds are summarised in Table 20 along with their 95% confidence limits. The area under the ROC plot (along with standard error [SE]) is given for each clinically important HIC threshold together with an SE calculated by the method of Hanley and McNeil⁴⁸ to give an approximate estimate of the uncertainty in the area.

Table 20: The sensitivity and specificity of liver R2 for biopsy HIC prediction

HIC threshold in mg Fe/g dry weight ($\mu\text{mol Fe/g dry weight}$)	Clinical relevance	Sensitivity (95% CI)	Specificity (95% CI)	Area under ROC plot (SE)
1.8 (32)	Upper 95% of normal	0.94 (0.86-0.97)	1.0 (0.88-1.00)	0.991 (0.008)
3.2 (57)	Suggested lower limit of optimal range for HICs for patients with transfusional iron overload treated with chelation therapy	0.94 (0.85-0.98)	1.00 (0.91-1.00)	0.988 (0.010)
7.0 (125)	Suggested upper limit of optimal range for HICs for patients with transfusional iron overload beyond which there is an increased risk of iron-induced complications	0.89 (0.79-0.95)	0.96 (0.86-0.99)	0.991 (0.009)
15.0 (269)	Threshold for greatly increased risk for cardiac disease and early death in patients with transfusional iron overload	0.85 (0.70-0.94)	0.92 (0.83-0.96)	0.982 (0.0016)

Figure 11 compares the HIC values estimated using R2-MRI data analysis with the HIC values estimated by chemical assay of a liver sample collected by needle biopsy in 73 patients who had extent of fibrosis assessed. The R2-HIC values are derived using the calibration curve shown in Figure 10. The solid line is a straight line fitted through the origin and it has a gradient of 0.980 ± 0.018 . The different data symbols in the figure differentiate between the different fibrosis stages: stages 0 and 1, \circ ; stages 2 to 4, \square ; and stages 5 and 6, \diamond .

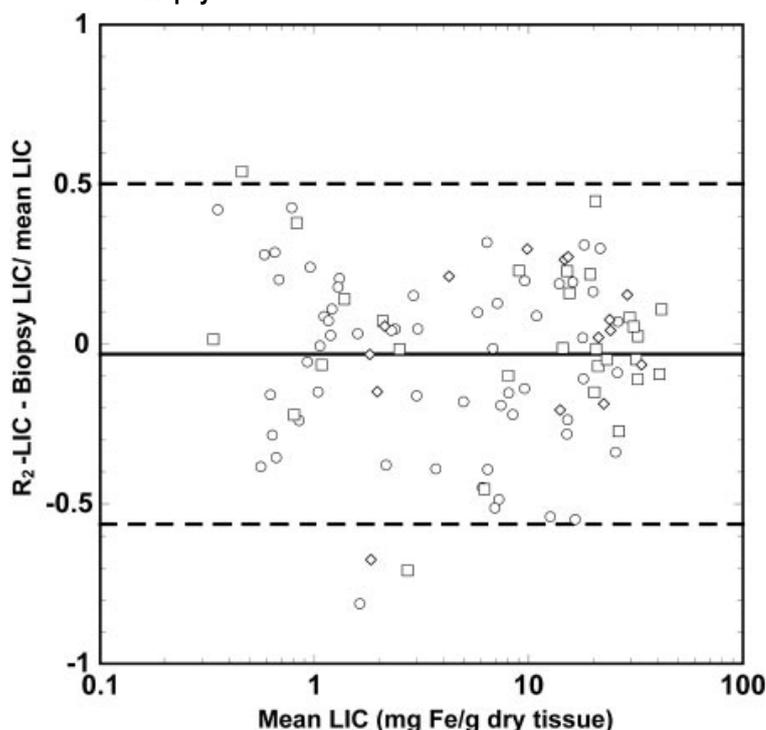
Figure 11: R2-HIC versus biopsy HIC as reported by St Pierre et al., 2005



Analysis of the data was performed using the methods of Bland and Altman to compare the R2-HIC values and biopsy HIC values for each of the individual subjects. In a Bland Altman plot, the relative difference between two measures for the same subject are plotted against the mean of the measures⁴⁷. Results for the relative difference between the two measurements of HIC are illustrated in Figure 12. The solid horizontal line in the figure shows the mean relative difference between the two measurements, and the

dashed lines indicate the upper and lower 95% limits of agreement around this mean relative difference. As with the presentation of data used to derive the calibration curve (Figure 10), different data symbols are used in Figure 12 to distinguish the different fibrosis stages: stages 0 and 1, ○; stages 2 to 4, □; and stages 5 and 6, ◇.

Figure 12: Bland Altman plot showing the differences (in relative terms) between HIC assessed by R2-MRI data analysis and HIC assessed by chemical assay of a liver sample taken by needle biopsy



The study reports that the 95% limits of agreement between R2-HIC and biopsy HIC were found to be 50% and -56%¹. This could be interpreted to indicate that, in approximately 95% of cases, the HIC measurement obtained by R2-MRI data analysis will be at most 50% higher or at least 56% lower than the HIC measurement derived by chemical assay of a liver sample from needle biopsy for the same subject. St Pierre et al. note that these limits of agreement are comparable with the expected repeatability coefficient of 53% between two needle biopsy HIC measurements from different parts of a fibrosis-free liver (based on an average coefficient of variation of needle biopsy HIC measurements from a single liver of 19% for biopsy specimens of <4 mg dry tissue).

The study found that the mean relative difference between HIC estimated by R2-MRI data analysis and HIC estimated by chemical assay of a liver sample taken by needle biopsy is not significantly different from zero for both the complete subject group and for the subgroups by stage of fibrosis. Consequently, St Pierre et al. suggest that the single calibration curve is sufficient to model the relationship between liver R2 and HIC for all the subject groups.

Reproducibility of results was assessed in ten patients. Subjects included three healthy volunteers with hepatitis, five patients with thalassaemia major, and two with hereditary

¹ As MRI uncertainty scales with iron loading, all values were expressed as percentage differences.

haemochromatosis. Each volunteer had R2 measured on two MRI scanners (both Siemens Magnetom Vision) on consecutive days. The entire cross-section of the largest liver slice was used for the determination of the mean R2 value in each case. The random uncertainty on a single slice mean liver measurement is reported to be $\pm 7.7\%$, with a nonsignificant systematic difference between the scanners of 1.2% (and a systematic difference of $<6.7\%$ with 95% confidence).

Key uncertainties

The following uncertainties were noted with respect to the evidence concerning accuracy of assessment of HIC by R2-MRI data analysis compared with liver biopsy:

- St Pierre et al. use the same set of data to
 - derive a calibration curve to convert average R2 measurements to an HIC (as shown in Figure 10); and
 - to compare the HIC values estimated using R2-MRI data analysis with the HIC values estimated by chemical assay of a liver sample collected by needle biopsy (Figure 11 and Figure 12).

The Advisory Panel concluded that although the derived calibration curve could form the basis for a hypothesis of the relationship between HIC and R2 values, for the validity of the relationship to be accepted, assessments of HIC by liver biopsy and by R2 should be conducted in a separate group of patients and the same relationship found to apply.

- St Pierre et al. consider that because the mean relative difference between HIC estimated by R2-MRI data analysis and HIC estimated by chemical assay of a liver sample taken by needle biopsy is not significantly different from zero (see Figure 12), the single derived calibration curve will be sufficient to model the relationship between liver R2 and HIC for all the subject groups. Issues in relation to this claim are as follows:
 - It is not surprising the mean relative difference between HIC estimated by R2-MRI data analysis and HIC estimated by chemical assay of a liver sample taken by needle biopsy is not significantly different from zero because, as noted previously, the same data are used to generate the calibration curve as to assess the relative difference between R2-MRI HIC and biopsy HIC.
 - The claim ignores the degree of variability in the mean relative difference between R2-MRI HIC and biopsy HIC. As shown in Figure 12, the 95% limits of agreement between R2-HIC and biopsy HIC were found to be 50% and -56%.
- It is not clear that sufficient investigation has been conducted to determine if the calibration curve is applicable to patients in relevant subgroups; e.g., patients with hereditary haemochromatosis versus patients with transfusional iron overload (given the difference in distribution of iron in parenchymal cells versus the reticuloendothelial system); adults versus children; across the different levels of fibrosis; patients on chelation therapy versus those not on chelation therapy. It has been postulated by Wood et al⁵⁰ that as iron chelation is not uniformly

effective across all tissue compartments, this may systematically alter iron storage size and distribution, potentially creating chelator-specific alteration in the relaxivity-iron calibration curves. To test this hypothesis, a study was conducted in gerbils. Two drug-specific shifts were observed in the liver calibration curves and were associated with changes in tissue water content, histology, or iron distribution. The authors found that the most clinically relevant observation was the deferasirox-induced shift in the liver R2-iron curve since R2-based iron estimates are being used to guide chelation therapy in iron overloaded patients. The explanation of this is evident from the histology. Deferasirox selectively eliminated iron from the hepatocytes, leading to a predominance of iron stored in larger depots (Kupffer cells and phagocytic aggregates). These residual deposits produce field defects larger than the scale of water diffusion during R2 measurement, producing static refocusing and decreased signal decay per milligram of iron. The study found that the other chelators produce a more balanced depletion of the different pools (iron length-scales) and did not exhibit a similar bias. This work also demonstrated that the severity and/or chronicity of iron loading influence MRI iron calibration curves. Animals who were acutely iron-loaded exhibited significant biases in R1 and R2 calibration curves independent of chelation therapy.

Conclusion

It appears that, as demonstrated by Table 20, assessment of HIC by R2-MRI data analysis can be used to provide a reliable indication of the range within which the true HIC is likely to lie. The Advisory Panel noted that the same conclusion would be applicable to chemical assay of a liver biopsy sample.

The evidence available is insufficient to reliably conclude that the estimation of hepatic iron concentration values generated by the FerriScan® technology is accurate in an absolute sense. There is substantial uncertainty concerning the validity of the assumed specific mathematical relationship assumed to exist between R2 and HIC by the FerriScan® software program. The benefit to clinicians of converting R2 values to HIC has to be weighed against the potential for false confidence in the accuracy of the HIC value generated. The Advisory Panel proposed that specification of reference ranges for R2 would be more helpful than conversion of R2 values to HIC (e.g., values of R2 up to $x\text{s}^{-1}$ are normal; values of R2 above $y\text{s}^{-1}$ indicate that the patient should commence treatment with chelation therapy; and values of R2 above $z\text{s}^{-1}$ indicate that the patient is at increased risk of iron overload-associated complications). Specification of reference ranges for R2 would be consistent with the approach adopted for measurements of other relaxometry metrics (e.g., $T2^*$, which is not converted to an equivalent tissue iron concentration but rather reported in units of s^{-1} and the result compared against a set of reference ranges). The Advisory Panel noted that potential problems arose because different approaches may generate different values for R2 such that different reference ranges might apply depending on the approach to determination of R2. This could potentially cause confusion in practice. However, the Advisory Panel also noted that there are many precedents for different assays to measure the same parameter with different reference ranges.

Does it change patient management?

As discussed in the section titled ‘Review of literature’ (commencing on p. 21), the literature search did not identify any published articles that would assist to address the

question as to whether information from R2-MRI data analysis would result in changes in patient management.

However, the application to MSAC requesting subsidy of R2-MRI data analysis did include one report of an unpublished study that it claimed was relevant to this question. The hypothesis of the study was that monitoring of HIC with FerriScan® would help reduce the body iron burden in transfused patients through improved quantitative feedback of chelator efficiency to both clinician and patient.

The study provided and assessed below is:

Patton N, Tapp H, Taylor J, Brown G, St Pierre T. The effect of access to non-invasive liver iron concentration measurements on patients at risk of iron overload from multiple blood transfusions: an audit and retrospective study.

Study design

The study consists of retrospective audit of the medical records of all subjects referred to the Radiology Department of the Royal Adelaide Hospital from the Royal Adelaide Hospital and the Women's and Children's Hospital for assessment of HIC by R2-MRI data analysis.

The stated aim of this study is to determine if the body iron burden in a consecutive cohort of multiple transfused patients in South Australia improved after providing access to non-invasive measurement of HIC using FerriScan®. The report by Patton et al. claims that the study tests the following hypotheses:

- The iron burden of the cohort was significantly less at last FerriScan® compared with at first FerriScan®.
- The proportion of patients in the cohort with HIC in the range associated with elevated risk of iron-related organ damage (>7 mg Fe/g dry tissue) decreased significantly from first FerriScan® to last FerriScan®.
- The proportion of patients in the cohort with HIC in the range associated with a greatly increased risk of cardiac disease and early death (>15 mg Fe/g dry tissue) decreased significantly from first FerriScan® to last FerriScan®.

Patient characteristics

The inclusion criteria for the study were:

- subject must be diagnosed with a haemolytic anaemia or ineffective haematopoiesis;
- subject must have received multiple blood transfusions prior to first FerriScan® measurement;
- subject must have had at least two FerriScan® measurements within a five-year period; and
- the date of the last FerriScan® measurement made on the subject must be at least 12 months after the first FerriScan® measurement made on the subject.

The baseline characteristics for patients included in the study are summarised in Table 21.

Table 21: Demographics and characteristics of patients included in the study conducted by Patton et al.

Patient characteristic	N=40
Transfusion-dependent	100%
Median age at first R2-MRI analysis (range)	28.8 (1.4-77.4)
Median age at last R2-MRI analysis (range)	32.3 (4.4-78.4)
Sex	
Females:	21/40 (52.5%)
Males:	19/40 (47.5%)
Median number of R2-MRI analyses (range)	5 (2-9)
Median period between first and last R2-MRI analysis in years (range)	3.4 (1.0-6.1)
Total number of R2-MRI measurements	196
Chelation therapy at time of initial R2-MRI scan	
• No therapy	7
• Desferrioxamine	33
Patient diagnosis	
• Thalassaemia major	25
• Diamond Blackfan anaemia	3
• Haemoglobin E /thalassaemia	2
• β^0/β^+ thalassaemia and hereditary persistence of foetal haemoglobine	2
• Thalassaemia intermedia	2
• Myelodysplastic syndrome	2
• Congenital dyserythropoetic anaemia	1
• Haemoglobin H (- α -)	1
• Haemoglobin H/Constant Spring	1
• Sickle cell anemia	1

Outcomes assessed and methods of analysis

Outcomes assessed in this study include:

- HIC levels estimated by R2-MRI over time
- Serum ferritin levels over time
- Change in proportion of subjects with
 - HIC >15 mg Fe/g dry tissue
 - HIC >7 mg Fe/g dry tissue
 - serum ferritin >1500 $\mu\text{g/L}$
 - serum ferritin >2500 $\mu\text{g/L}$
 - 12-month averaged serum ferritin >1500 $\mu\text{g/L}$
 - 12-month averaged serum ferritin >2500 $\mu\text{g/L}$
- Change in chelation therapy over time

HIC by R2-MRI analysis and serum ferritin levels are log-normally distributed. The means of the initial and final R2-MRI analysis and the means of serum ferritin averaged over the 12 months prior to initial and final R2-MRI analysis were compared using Student's t-test.

The thresholds for HIC used to classify patients (i.e., >15 mg and >7 mg Fe/g dry tissue) in this study are adopted on the basis of information reported by Oliveri et al. (1997)⁵¹. Oliveri et al. report that HICs greater than 15 mg Fe/g are associated with a greatly increased risk for cardiac disease and early death for patients with transfusional iron overload, and that those at 7 mg Fe/g are at the suggested upper limit of optimal range for HICs for transfusional iron overload.

Similarly, the thresholds for serum ferritin used to classify patients in this study are adopted on the basis of information reported by Oliveri et al. (1994)⁵². This publication reports that those patients who recorded most of their serum ferritin concentrations at less than 2,500 µg/L had an estimated cardiac disease-free survival of 91% after 15 years. This was in contrast to those patients who recorded most of their serum ferritin concentrations in excess of 2,500 µg/L, and who had an estimated cardiac disease-free survival after 15 years of less than 20%.

Results

Table 22 summarises the results reported by Patton et al.

Table 22: Results reported by Patton et al.

Outcome	At initial FerriScan® N=40	At final FerriScan® N=40	Difference
Chelation therapy at time of initial R2-MRI scan			
• No therapy	7	2	-5
• Desferrioxamine	33	16	-17
• Desferrioxamine & deferiprone		1	+1
• Deferasirox		20	+20
• Desferrioxamine & deferasirox		1	+1
HIC by R2-MRI analysis			
- Geometric mean in mg Fe/g dry tissue (range)	6.8 (0.5-41.3)	4.8 (0.9-40.1)	-2.0 (p=0.008)
Proportion of patients with HIC by R2-MRI:			
>15 mg Fe/g dry tissue	14/40 (35%)	5/40 (12.5%)	-22.5% (p=0.01)
> 7 mg Fe/g dry tissue	20/40 (50%)	14/40 (35%)	-15% (p = n.s.)
Serum ferritin levels			
- Geometric mean in µg/L (range)	1502 (253-9940)	1389 (266-4291)	-113 (p= n.s.)
Serum ferritin levels*			
> 2500 µg/L	11/40 (25%)	11/40 (25%)	0 (p= n.s.)
> 1500 µg/L	18/40 (45%)	19/40 (47.5%)	+2.5% (p= n.s.)
12 month averaged serum ferritin levels#			
- Geometric mean µg/L (range)	1541 (243-9903)	1442 (239-5157)	-99 (p =n.s.)
12 month averaged serum ferritin levels #			
> 1500 µg/L	18/40 (45%)	17/40 (42.5%)	-2.5% (p = n.s.)
>2500 µg/L	10/40 (25%)	12/40 (30%)	+5% (p = n.s.)

n.s. = non-significant

* Those closest to R2-MRI measurement used but only if within 30 days (162 pairs of HIC and SeFe available for comparison)

12 month period immediately preceding 1st R2-MRI analysis and immediate preceding the final R2-MRI data analysis were calculated where values were available

A total of 19 clinical decisions were documented in the case notes as being based on HIC results. These decisions comprised initiation of chelation therapy, increasing chelator dose, decreasing chelator dose, and change of mode of delivery of desferrioxamine from subcutaneous to intravenous.

On the basis of results presented in Table 22, Patton et al. claim that the significant decreases in the body iron burden, together with the documented clinical decisions regarding chelation therapy based on the HIC results, support the hypothesis that introduction of non-invasive monitoring of HIC can lead to a decreased body iron burden through improved clinical decision making and improved feedback to patients, and hence improved adherence to chelation therapy. The study authors also conclude that the inability of serum ferritin measurements to detect the drop in body iron burden of the cohort is most likely due to the test's poor sensitivity and specificity of serum ferritin concentration.

Discussion

- The study conducted by Patton et al. has several design limitations which are likely to result in substantial confounding to the interpretation of results:
 - The study does not include information for a comparator arm, i.e., it is not possible to determine what results would have been observed in the absence of HIC by R2-MRI. It is therefore not possible to determine whether the observed changes in HIC and chelation therapy are due solely to patients receiving R2-MRI data analysis to guide their treatment or due to other reasons. It is possible that the same clinical decisions would have been made on the basis of serum ferritin results and clinical assessment (e.g., changes in symptomatology).
 - Specific changes made to a patient's management are not documented in either the report nor the spreadsheet provided by the sponsor that records individual patient records (e.g., increase dose of chelator, decrease dose of chelator, change of chelator)
 - The study results are potentially confounded by:
 - changes in patient education efforts;
 - changes in the availability of chelating agents. It is notable that no patients were being treated with deferasirox at the start of the study but that several patients commenced therapy with deferasirox (21/40) over the course of the study. Deferasirox became available as a PBS benefit in December 2006. The data collection for this study related to the period between 31 December 2001 and 8 April 2008. It is possible that several patients switching to deferasirox were previously non-compliant with recommended therapy and the new availability of deferasirox led to an improvement in their management.

Conclusion

It may be likely that more accurate information about a patient's liver iron concentration would result in more appropriate management of patients (e.g., more appropriate dosing of chelation therapy and closer surveillance of high-risk patients). However, there is currently no evidence available that convincingly demonstrates or quantifies the extent to which that use of analysis of R2 data to assess the extent of iron overload in a patient will change the patient's management.

A study reported by Kidson-Gerber et al. (2008)⁵³ demonstrated that adherence to chelation therapy was a major issue. The extent to which greater information about extent of iron overload will result in improved compliance is unknown.

Does change in management improve patient outcomes?

Phlebotomy is the accepted treatment for management of patients with hereditary haemochromatosis and chelation therapy is the accepted treatment for treating transfusional iron overload. The use of such interventions to manage or prevent iron overload is well established in these conditions. Therapeutic venesection for the management of haemochromatosis is reimbursed under the MBS (MBS Item 13757) and chelating agents are reimbursed under the PBS (desferrioxamine, deferiprone and deferasirox). This assessment assumes that the effectiveness of these therapies is not in dispute and that a change in management to better guide therapy will be associated with improved patient outcomes.

Summary of effectiveness

It appears that, as demonstrated by Table 20, assessment of HIC by R2-MRI data analysis can be used to provide a reliable indication of the range within which the true HIC is likely to lie. The Advisory Panel noted that the same conclusion would be applicable to chemical assay of a liver biopsy sample.

The evidence available is insufficient to reliably conclude that the estimation of hepatic iron concentration values generated by the FerriScan® technology is accurate in an absolute sense. There is substantial uncertainty around the validity of the assumed specific mathematical relationship assumed to exist between R2 and HIC by the FerriScan® software program. The benefit to clinicians of converting R2 values to HIC have to be weighed against the potential for false confidence in the accuracy of the HIC value generated. The Advisory Panel proposed that specification of reference ranges for R2 would be more helpful than conversion of R2 values to HIC; e.g., values of R2 up to xs^{-1} are normal; values of R2 above ys^{-1} indicate that the patient should commence treatment with chelation therapy; and values of R2 above zs^{-1} indicate that the patient is at increased risk of iron overload-associated complications.

It may be likely that more accurate information about a patient's liver iron concentration would result in more appropriate management of patients (e.g., more appropriate dosing of chelation therapy and closer surveillance of high-risk patients). However, there is currently no evidence available that convincingly demonstrates or quantifies the extent to which that use of analysis of R2 data to assess the extent of iron overload in a patient will change the patient's management.

Other relevant considerations

Consumer implications and other considerations

There are potential issues concerning equity of access because, in order to access this technology, patients must attend a facility with a licensed MRI machine.

What are the economic considerations?

Economic evaluation

Key results

Assessment of HIC by R2-MRI data analysis will generally substitute for assessment of HIC by chemical assay of a liver biopsy sample. A comparative cost analysis of the two procedures is presented.

For patients who currently do not have assessment of liver iron by liver biopsy but who might have an assessment conducted by R2-MRI data analysis, it was considered that, if R2-MRI data analysis was found to be less costly than liver biopsy, then it would be reasonable to assume that R2-MRI data analysis is acceptably cost-effective. This is based on the grounds that liver biopsy is indicated in these patients and could theoretically be used.

Costs associated with assessment of HIC by R2-MRI data analysis

A cost of \$600.00 per assessment of HIC by R2-MRI data analysis is assumed. For comparison, the MBS fee, at 1 July 2010, for Item 63482 – MRI scan of the pancreas and biliary tree – is \$403.20. Assuming a similar fee for the MRI component of this intervention suggests the applicant is seeking a fee of \$196.80 for the computerised quantitative analysis of data collected by MRI.

With FerriScan®, a telemedicine model is adopted, whereby data are transmitted to a central data analysis facility as a digital specimen to be analysed. Following analysis at the central facility, a report detailing results is returned to the radiologist at the centre where the MRI was conducted. Alternate approaches might involve the distribution of software (e.g., by licence) to individual MRI centres for direct use by individual radiologists to assess HIC by R2-MRI data analysis. The latter approaches may be associated with lower costs for analysis of R2-MRI data.

It is assumed that there would be marginal difference between the MBS fee for assessment of HIC by R2-MRI data analysis and the fee charged in practice. This assumption is made on the grounds that the average government cost for MBS Item 63482 – MRI scan of the pancreas and biliary tree – is \$344.41, which is approximately 85.4% of the schedule fee.

Some additional costs may be incurred for patients requiring sedation (MBS Item 63494 with an associated fee of \$44.80) or anaesthesia (MBS Item 63497 with an associated fee of \$156.80). No information was available in the public domain or in the application to MSAC to determine the extent to which these associated items would be used.

Costs associated with assessment of HIC by chemical assay of a liver biopsy sample

Table 8 summarises the MBS items that are likely to be associated with assessment of HIC by chemical assay of a liver biopsy sample. It is notable that, although the safety of liver biopsy is enhanced by ultrasound guidance, no specific MBS item for ultrasound-guided liver biopsy is included. In practice, it is likely that the procedure would be

performed with ultrasound guidance. The costs for ultrasound guidance were estimated assuming MBS Item 55036 would be applicable. Costs to the MBS for chemical assay of a liver biopsy sample are likely to be approximately \$345.10. This is estimated by assuming delivery of one of each of the services listed in Table 8 and assuming the average MBS expenditure per item as incurred in 2009. According to calculations of MBS expenditure per item, it appears that anaesthetic services are associated with safety net impact but the impact from the safety net for items is more marginal.

Liver biopsy is generally performed under sedation in a hospital; therefore, costs associated with hospitalisation also need to be taken into account when taking a health care system perspective. The average cost for a liver biopsy performed in hospital on a day-stay basis, without radiological guidance, has been estimated to be \$1032.00 at Liverpool Hospital, South Western Sydney Area Health Service⁵⁴.

Theoretically, costs associated with the management of complications should also be factored in estimation of costs associated with assessment of HIC by chemical assay of a liver biopsy sample. However, as the rate of complications is small, around 0.5% for ultrasound-guided liver biopsy, it was considered that such costs were likely to have minimal impact on the estimated overall cost associated with the procedure.

Table 23: MBS items associated with chemical assay of a liver biopsy sample

Item	Description and fee [^]	MBS expenditure in 2009	MBS services in 2009	Average expenditure per service in 2009
20702	Initiation of management of anaesthesia for percutaneous liver biopsy (4 basic units) Fee: \$73.20	\$14,949	158	\$94.61
30409	Liver biopsy, percutaneous (Anaes.) Fee: \$161.20	\$312,904	2,437	\$128.40
55036	ABDOMEN, ultrasound scan of, including scan of urinary tract when undertaken but not being a service associated with the service described in item 55600 or item 55603, where: (d) the patient is referred by a medical practitioner for ultrasonic examination not being a service associated with a service to which an item in Subgroups 2 or 3 of this Group applies; (e) the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member; and (f) the service is not performed with item 55038, 55044 or 55731 on the same patient within 24 hours (R). Fee: \$111.30	\$55,878,102	579,997	\$96.34
66831	Quantitation of copper or iron in liver tissue biopsy Fee: \$31.15	\$2,240	87	\$25.75

[^] Source: August 2009 Medicare Benefits Schedule

Overall conclusion with respect to cost-effectiveness

Assessment of HIC by R2-MRI data analysis is likely to be cost-saving from a health care perspective compared with assessment of HIC by chemical assay of a liver biopsy sample.

However, since costs of hospitalisation are not borne by the MBS, the assessment of HIC by R2-MRI data analysis is likely to be more costly to the MBS than chemical assay of a liver biopsy sample.

Financial analysis

The prevalence of haemochromatosis in a sample of healthy individuals in Australia has been reported to be at least 0.36%, or 1:284 individuals⁵⁵. Extrapolating to an Australian population of 22,000,000, it can be estimated that approximately 77,500 Australians have haemochromatosis. It has been suggested that approximately 60% of patients (which corresponds to 46,500 Australian patients) with hereditary haemochromatosis will eventually develop iron overload. However, a substantial proportion of patients will be undiagnosed because no screening program is in place to detect hereditary haemochromatosis. In the year ending 31 December 2009, 51,250 tests (MBS Item 73317) for the genetic mutation associated with haemochromatosis were performed on patients at high risk for haemochromatosis. Unfortunately, the risk of disease for those with a genetic predisposition has not been elucidated in the literature. Powell et al. (2006) report that screening for haemochromatosis was offered to relatives of 259 patients with proven C282Y-associated haemochromatosis. Unfortunately, the authors do not report the total number of relatives tested. They do report that 401 relatives were identified as being homozygous for the genetic mutation for haemochromatosis and that 69 (17%) of these demonstrated a disease-related clinical condition. In a similar study reported by Bulaj et al. (2000), 25% of identified subjects demonstrated at least one disease-related condition. Assuming the average number of relatives tested per patient with proven haemochromatosis was between 5 and 50, an incidence of genetic mutation of between 3% ($401/(259 \times 50)$) and 30% ($401/(259 \times 5)$) can be estimated for a high-risk population. Applying these proportions, it can be estimated that the number of patients likely to be diagnosed with haemochromatosis and demonstrating some clinical condition per year in Australia will be between 265 ($51,250 \times 3\% \times 17\%$) and 3850 ($51,250 \times 30\% \times 25\%$).

No reports of the prevalence of haemoglobinopathies requiring regular transfusion (e.g., thalassaemia major) in the Australian population were located. However, the Advisory Panel suggested that there would be approximately 500 patients with haemoglobinopathies in Australia who would have a need for regular monitoring of HIC.

Most patients with MDS are elderly (median age range 65 to 70 years). As a consequence, the incidence and prevalence of these diseases are rising as the population ages. The incidence of MDS from 2001 to 2003 was 3.3 per 100,000 in the USA⁵⁶. Assuming a survival rate of 45% at three years, a prevalence of approximately 10 per 100,000 can be estimated. This suggests that, in an Australian population of 22,000,000, approximately 2,200 patients are affected by MDS. The prevalence of iron overload in patients with MDS is not well described. List (2010)⁵⁷ reports that between 50% and 80% of patients

with MDS receive transfusions. Patients with higher risk MDS are more frequently dependent upon transfusions than patients with lower risk MDS (68% vs 22%). However, patients with lower risk MDS may survive five years or longer, and with time may be at greater risk of iron overload. Assuming 50% of MDS patients are at risk of transfusional iron overload, it can be estimated that approximately 1,100 patients would be candidates for monitoring of HIC.

In total, considering patients with haemochromatosis, patients with haemoglobinopathies and patients with MDS, the likely number of patients per year to have assessment of HIC by R2-MRI data analysis is estimated to be between 1,865 and 5,450 (assuming restrictions on frequency of use as included in Table 3 and Table 4). Assuming a cost of \$600.00 per year for assessment of HIC by R2-MRI data analysis, the total financial implications of making this intervention available on the MBS is estimated to be between \$1.1 million and \$3.3 million. It is assumed that there would be little difference between the MBS fee and the fee charged in practice. This assumption is made on the grounds that the average government cost for MBS Item 63482 – MRI scan of the pancreas and biliary tree – is \$344.41, which is approximately 85.4% of the scheduled fee of \$403.20. Taking only the MBS perspective and assuming negligible impact from the safety net, the financial implications for the MBS could be estimated to be between \$0.9 million and \$2.8 million. No cost-offsets for reduced use of liver biopsy are included in these calculations.

Some additional costs may be incurred for patients requiring sedation (MBS Item 63494 with an associated fee of \$44.80) or anaesthesia (MBS Item 63497 with an associated fee of \$156.80). No information was available to determine the extent to which these associated items would be used.

Appendix A MSAC terms of reference and membership

The Medical Services Advisory Committee (MSAC) is an independent scientific committee comprising individuals with expertise in clinical medicine, health economics and consumer matters. It advises the Minister for Health and Ageing on whether a new medical service should be publicly funded based on an assessment of its comparative safety, effectiveness, cost-effectiveness and total cost, using the best available evidence. In providing this advice, MSAC may also take other relevant factors into account. This process ensures that Australians have access to medical services that have been shown to be safe and clinically effective, as well as representing value for money for the Australian health care system.

MSAC is to:

- Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures, in relation to:
 - the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
 - whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
 - the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
 - the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
 - other matters related to the public funding of health services referred by the Minister.
- Advise the Australian Health Minister's Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to such sub-committees.

The membership of MSAC at the *July 2010* meeting comprised a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Professor Robyn Ward (Chair)	Medical Oncology
Associate Professor Frederick Khafagi (Deputy Chair)	Nuclear Medicine
Professor Jim Butler (Chair, Evaluation Sub-committee)	Health Economics
Associate Professor John Atherton	Cardiology
Professor Justin Beilby	General Practice/Research
Associate Professor Michael Bilous	Anatomical Pathology
Professor Jim Bishop AO	Chief Medical Officer (<i>ex officio member</i>)
Professor Peter Cameron	Trauma and Emergency Medicine
Associate Professor Kirsty Douglas	General Practice/Research
Professor Kwun Fong	Thoracic Medicine
Professor Richard Fox	Medical Oncology
Professor John Horvath	Renal Medicine/Health Workforce
Ms Elizabeth Koff	Health Administration
Professor Helen Lapsley	Health Economics
Professor Peter McCluskey	Ophthalmology
Mr Russell McGowan	Consumer Health Representative
Dr Allan McKenzie	Radiology
Dr Graeme Suthers	Genetics/Pathology
Mr David Swan	AHMAC Representative (<i>ex officio member</i>)
Professor Ken Thomson	Radiology
Dr Christine Tippet	Obstetrics/Gynaecology
Associate Professor David Winlaw	Paediatric Cardiothoracic Surgery
Dr Caroline Wright	Colorectal Cancer

Appendix B Advisory Panel and health technology assessors

Advisory Panel – MSAC application No. 1131–Assessment of liver iron by MRI data analysis

Member	Nomination / Expertise or Affiliation
Prof Richard Fox (Chair)	Member of MSAC (and oncologist)
A/Prof Rob Lindeman	Haematologist
Dr Barbara Leggett	Gastroenterologist
Dr Stephen Drew	Nominee from Royal Australian and New Zealand College of Radiologists (RANZCR)
Ms Jane Lampitsi	Nominee from Consumers' Health Forum of Australia

Evaluation Sub-committee input

Prof Andrew Wilson	Member of Economics Sub-Committee of MSAC (clinical medicine/public health)
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Evaluators

Name	Organisation
Sandra Younie	Deakin Health Economics, Deakin University
Bridie Murphy	Deakin Health Economics, Deakin University
Liliana Bulfone	Deakin Health Economics, Deakin University

Glossary and abbreviations

DHE	Deakin Health Economics
DoHA	Department of Health and Ageing
Fe	Iron
g	Gram
HIC	Hepatic iron concentration
hrs	Hours
kg	Kilogram
L	Litre
MBS	Medicare Benefits Schedule
MDS	Myelodysplastic syndrome
mg	Milligram
mM	Millimole
MnCl ₂	Manganese chloride
MRI	Magnetic resonance imaging
ms	Milliseconds
MSAC	Medical Services Advisory Committee
ng	Nanogram
PBS	Pharmaceutical Benefits Scheme
ROC	Receiver operating characteristic
SD	Standard deviation
SE	Standard error
SQUID	Superconducting quantum interference device
SSE	Single spin-echo
TE	Spin-echo time
TGA	Therapeutic Goods Administration
TR	Pulse repetition time
UK	United Kingdom
USA	United States of America
µg	Microgram

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