FerriScan®
MRI Measurement of Liver Iron Concentration

FAQ on FerriScan® asked by clinical communities

We measure cardiac T2* of our patients, why is it important to measure liver iron concentration (LIC) as well?

Measuring cardiac T2* is important as a significant number of transfused patients die from cardiac complications. However, the risk of cardiac complications is decreased if the total body iron store is accurately monitored and treated. The key reasons why LIC measurement is important are:

1) The LIC value is the best measurement of total body iron stores. [1]
2) Under normal circumstances, the liver is the primary site of iron storage. However, once a certain threshold of liver iron is exceeded, iron begins to accumulate in the heart and other organs. [4]
3) High LIC acts as an early warning sign of possible future cardiac complications, as it may prospectively predict cardiac iron loading and cardiac disease.[2,3]
4) FerriScan enables clinicians to determine the effectiveness of chelation therapy and when to adjust the therapy accordingly, minimising the risk of iron loading in other organs.

How does FerriScan work?

FerriScan is an MRI-based technology that works by analysing abdominal images acquired by MRI scanners that have been set up with the FerriScan protocol. This requires no new equipment, software or training and is provided as an image analysis service charged only per analysis. The image data acquired during the MRI scan are uploaded to the Company's secure server for analysis at the central FerriScan Service Centre. Within two business days a "Liver Iron Concentration" (LIC) report is produced and made available to the MRI Centre.

What information does the LIC report provide?

The LIC report provides:

- the patient's liver iron concentration
- a table to indicate the clinical relevance of their LIC measurement
- a map of the iron distribution across their liver
- a histogram showing indicative iron distribution
- where available, historical data showing the patient's progress over time

Can FerriScan be used to assess iron in the heart?

FerriScan itself does not measure iron in the heart. However, a cardiac T2* measurement can also be provided in conjunction with a FerriScan where the MRI scanner is suitably equipped to capture cardiac data.

What are the advantages of using FerriScan?

- Proven accuracy
- Reliability across different centres and scanners, in the presence of inflammation, fibrosis or cirrhosis
- Standardised image analysis process
- A quality-controlled process. All FerriScan analyses are conducted in an ISO-13485 certified central facility
- MRI scanners using FerriScan are regularly assessed against a Phantom(quality standard) to ensure reliability

Why is FerriScan better than alternative tests?

FerriScan vs liver biopsy

- Liver biopsy is an invasive and painful procedure which cannot be performed frequently
- There is a high risk of sampling error with biopsy due to significant heterogeneity of iron concentrations throughout the liver
- The biopsy results may also be affected by the presence of other liver diseases
- Liver biopsy may be contraindicated for some patients

FerriScan vs liver T2*

- Liver T2* refers to a variety of methodologies, each of which uses a calibration curve specific to that methodology and not transferable between methods. This renders the interpretation of T2* data into LIC measurements prone to error, particularly at high levels of iron loading.
- Liver T2* methods have generally been calibrated on one scanner only, with small patient populations, so inter-scanner and inter-operator variability is a significant issue. FerriScan was calibrated on five different makes or models of scanner with a patient population of 105 and independently validated in a further patient population of 233, across a range of iron-loading conditions [6, 7].
- Liver T2* methodologies lack the standardisation and validation of FerriScan. All FerriScan sites must verify their scanner set-up against a set of standards prior to starting patient scanning. A reverification is then performed every 12 months to ensure the scanner settings remain accurate.
- Studies have indicated that FerriScan results are not affected by the presence of liver fibrosis.
- Liver T2* requires a patient breath-hold, which may be difficult for paediatric or anxious patients to achieve, particularly if sedation is required. FerriScan requires no breath-hold and is therefore not impacted by these issues.

FerriScan vs Rennes (Gandon) method

- The Rennes method demonstrates only a weak correlation with liver biopsy in patients with a high LIC (above 11.2 mg/g dw) [5]. In comparison, FerriScan has regulatory clearance to measure LIC up to 43 mg/g/dw.

FerriScan vs Serum Ferritin

There is a weak correlation between serum ferritin and LIC as results are confounded by factors such as inflammation and infection. Serum ferritin is only a surrogate marker for LIC and therefore can only be used for monitoring trends in patients' iron loading.

Is FerriScan approved by regulatory bodies?

FerriScan has the following regulatory clearances:

- In the US by the FDA (Food and Drug Administration);
- In Australia by the TGA (Therapeutic Goods Administration);
- In Europe (CE Mark), which covers 27 countries.

In the rest of the world, FerriScan complies with local regulations. Resonance Health has an internal approval process to ensure all MRI centres wishing to offer FerriScan can legally and technically do so. The FDA has mandated the use of FerriScan or biopsy in patients with Non-Transfusion Dependent Thalassaemia who are being treated with the iron chelator Exjade, a medication which helps reduce body iron levels.

How long does FerriScan take?

The scan time for FerriScan is approximately 9-10 minutes. Results are then analysed and returned to the MRI Centre within a target time of two business days.

Is FerriScan clinically validated?

Yes. FerriScan was calibrated on a range of different makes or models of scanner with a patient population of 105 and independently validated in a further patient population of 233, across a range of different makes of MRI scanners, in different countries and in patients with a variety of iron-loading conditions. [6, 7]

How would this test help me provide better services to my patient?

The accurate assessment of iron loading provided by FerriScan helps inform clinician's decisions on patient management. The LIC result is provided with further information to provide clinical relevance to the result, including graphics to illustrate the distribution and range of iron loading across the liver section. The historical information provided on FerriScan LIC Reports has been found by clinicians to be a very useful aid to motivating patient compliance with their treatment regime.

Where is FerriScan available?

FerriScan is available in over 30 countries at more than 220 MRI centres around the world. Existing locations can be found on our website www.resonancehealth.com/find a centre/all

Does the MRI centre need to buy/install new software on the MRI scanner?

No. FerriScan is an image analysis protocol that can be implemented on most 1.5T MRI scanners using the scanner's own settings. A Phantom Pack (scanner setup verification tool) is provided to verify the scanner and patient scanning may then commence. FerriScan is provided as an image analysis service, charged only per analysis.

Is FerriScan reimbursed by Health Authorities or Private Insurers in my country?

In most countries the referring clinician will be able to advise patients about possible reimbursement. FerriScan is reimbursed in the following countries.

- **USA**
  Some insurers offer cover on a pre-approved or case by case basis in certain states. Medicare / Medicaid coverage is also available for some patients. Referring clinicians or FerriScan MRI centres have more information available on local reimbursement policies.
- **Canada**
  FerriScan is reimbursed by the "Out-of-country" health service in a number of territories. In Ontario, the treating clinician must forward an application of each patient to the individual provinces Ministry of Health (MOH) for approval. Once approved, the MOH will grant a timeframe for the patient to have their FerriScan. Other territories have slightly different arrangements.
- **United Kingdom**
  Many UK hospitals have gained reimbursement from their NHS Trust and referring clinicians or MRI centres will have more information on accessing this.
- **Germany**
  Case by case reimbursement for FerriScan may be available for certain patients.
- **Australia**
  While Medicare reimbursement is not available, FerriScan can in some cases be accessed through State-funded hospital services.
- **New Zealand**
  FerriScan is reimbursed in New Zealand by some District Health Boards.

Do MRI Centres need to receive any special training?

No. An instruction manual is provided to assist technicians set up the FerriScan protocol and scan the Phantom Pack (scanner setup and verification tool). Should further assistance be required, the FerriScan Service Centre will contact them by telephone or email to resolve any questions and ensure the centre is able to provide FerriScan services to their patients.

How is security of patient data assured?

Resonance Health has undertaken extensive measures to ensure the security of patient data. The measures include data and internet security, staff training, de-identification of patient data, quality control procedures, physical security systems within the Service Centre, and adherence to:

- Medical Technology Association of Australia (MTAA) Code of Practice
- AdvaMed – Advanced Medical Technology Association (USA) Code of Ethics

Resonance Health utilises its proprietary secure web-based system (FAST) for data upload, tracking, and result download. All data transfer to and from the FAST system is secured. Access to the system is restricted to authorised personnel by unique login IDs and passwords. Resonance Health's infrastructure is compliant with:

- Health Insurance Portability and Accountability Act (HIPAA) (USA)
- Health Information Technology for Economic and Clinical Health (HITECH) Act (USA)
- Data Protection Act (UK)
- Australian Privacy Act 1988
- Resonance Health is also a registered data controller in the UK registered with the Information Commissioner's Office.

What quality controls are in place?

All aspects of Resonance Health's service provision are performed in accordance with our certified quality management system. From the recruitment and training of staff, to the receipt of data and the quality control checking of results, documented procedures are followed and records retained.

A primary focus of the company is the continual improvement of the quality management system and the service we provide, through monitoring and actioning of customer feedback, internal audits, and a corrective and preventative action system. Our quality management system is certified to the following international standard:

- ISO 13485: Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes.

How cost-effective is FerriScan?

There are no set up costs for FerriScan; there is no equipment to purchase, software to install or training to be completed. FerriScan is charged per analysis only. A FerriScan requires no contrast agent, recovery time and generally no sedation.

By providing the most accurate and reliable measurement across all ranges of LIC normally encountered in clinical practice, FerriScan enables clinicians to optimise patient's treatment, basing dosage decisions on the patient's measured level of iron loading.

Which clinical authorities recommend the use of FerriScan?

- UK Standards of Care for Thalassaemia 2016
- TIF Guidelines for the Clinical Management of Thalassaemia 3nd Edition 2014
- 2012 Thalassemia Standards of Care Guidelines Northern California Comprehensive Thalassemia Network and Children's Hospital, Oakland
- 2012 Guidelines for the Care of Patients in the UHN Red Blood Cells Disorders Program University Health Network, Toronto General Hospital, Canada
- Cooley's Anemia Foundation 2012 Position Statement on MRI-Based Hepatic Iron Assessment Methods

- 2011 Australian Guidelines for the assessment of iron overload and iron chelation in transfusion-dependent thalassaemia major, sickle cell disease and other congenital anaemias.
- 2008 Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK, UK Sickle Cell Society
- Practice Guidelines for the Management of Iron Overload, 2008 Italian Society of Hematology
- Canadian Practice Guidelines for MDS, 2008

How do I get FerriScan established at my MRI Centre?

Ask your Radiologist to complete an MRI Centre Scanner Details Form (www.resonancehealth.com/information-for-radiology-centres/mri-scanner-details-form.html) to establish that their MRI scanner is suitable for FerriScan. Once this has been received by Resonance Health, we will work with the MRI Centre to verify their scanner for the FerriScan protocol and enable them to submit FerriScan image data for analysis.

References:

[1] Angelucci E et al, Hepatic iron concentration and total body iron stores in thalassemia major. NEng J Med 2000; 343:327-31

[2] Telfer P, et al, Hepatic iron concentration combined with long-term monitoring of serum ferritin to predict complication of iron overload in thalassemia major. British Journal of Haematology 2000; 110:971-77

[3] Noetzli L et al, Longitudinal analysis of heart and liver iron in thalassaemia major. Blood 2008; 112:2973-78

[4] Jensen PD et al, Evaluation of myocardial iron by magnetic resonance imaging during iron chelation therapy with deferrioxamine: indication of close relation between myocardial iron content and chelatable iron pool. Blood 2003; 101:4632-39.

[5] Rose C et al, Liver iron content assessment by routine and simple magnetic resonance imaging procedure in highly transfused patients. Eur J Haematology 2006; 77:145-49

[6] St Pierre T et al, Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. Blood 2005; 105:855-61.

[7] St Pierre T et al, Multi-Center Validation of Spin-Density Projection-Assisted R2-MRI for the Non-invasive Measurement of Liver Iron Concentration. Magn Reson Med. (2013), doi: 10.1002/mrm.24