

Iron Overload and How to Measure It - FAQ for Patients

What is “Iron Overload”?

When the body absorbs more iron than is required in normal daily usage, it has no natural mechanism to remove the excess iron. This may happen as a result of the body absorbing too much iron through the diet or where additional iron is introduced through regular blood transfusions in the treatment of disease. Surplus iron accumulates in the organs and tissues of the body, particularly the liver, potentially leading to liver fibrosis, liver cancer and death. Most cases of iron overload are the result of genetic conditions such as Thalassaemia, Sickle Cell Disease or Hereditary Haemochromatosis.

What is liver fibrosis?

Liver fibrosis is scarring of the liver. Like any other scars, this indicates that some damage has occurred. If the cause of the fibrosis is identified and early treatment provided, it is often possible for the damage to be reversed, otherwise further liver complications may ultimately occur.

How will my doctor assess whether I have iron overload, and why is FerriSmart® better than alternative tests?

If your doctor suspects that you have iron overload, an initial serum ferritin test will be ordered by your doctor. The results of this will indicate whether you have high levels of serum ferritin in your body. However, serum ferritin is only a surrogate marker for total body iron stores and can be affected by other conditions such as alcohol consumption, metabolic syndrome, obesity, diabetes, liver disease, malignancy, infection or inflammation. In addition serum ferritin saturates at higher liver iron concentrations, meaning that it is not useful to quantify iron overload. Therefore, it cannot be used alone for the diagnosis and clinical management of iron overload.

So what are the alternatives when a serum ferritin test result is high? Prior to FerriScan® and FerriSmart, which are R2-MRI based techniques for the quantification of liver iron concentration, the gold standard (or accepted ‘best practice’) method for estimating the extent of iron loading in the liver was through liver needle biopsy, which is an invasive and unpleasant surgical procedure. The need for anesthesia, patient monitoring and recovery time also makes it expensive. In addition, when a biopsy is taken, the sample size is only a very small fraction (1/5000) of the liver, which is subject to large sampling error for assessing liver iron levels, especially when the liver iron distribution is varied throughout the liver.

There are also several MRI-based methodologies known as T2* or Signal Intensity Ratio (SIR) that may be used to provide a T2* value and attempt to equate this to a liver iron concentration. There is a fundamental limitation of the T2* methods that causes them to fail at high liver iron concentrations. This, combined with the variability in results between different scanners and MRI centres, reduces significantly

the reliability of these methods. Additionally, these tests fail to offer the standardization and quality control systems offered by the FDA-cleared MRI-based products FerriScan® and FerriSmart.

What is an MRI?

Magnetic Resonance Imaging (MRI) is a technology that uses a magnetic field and pulses of radio wave energy to make pictures of organs and structures inside the body. In many cases, MRI gives different information about structures in the body than can be seen with an X-ray, ultrasound, or computed tomography (CT) scan.

Why do I need an MRI scan to measure my liver iron concentration?

An MRI scan allows detailed information to be gathered about the body's organs without the need for invasive surgical procedures such as liver biopsy. The FerriSmart® images show an entire cross-section of the liver and allow a more accurate evaluation of the liver as compared to liver biopsy.

What is FerriScan®?

FerriScan® is an MRI-based, non-invasive test for the measurement of Liver iron Concentration (LIC) in patients who may be suffering from liver iron overload. FerriScan®, which was originally calibrated against liver biopsy, is now considered the gold-standard in the measurement of LIC, has been established in over 450 prestigious hospital centres across the globe, and is included in numerous international clinical guidelines. It has been used by both leading clinicians and pharmaceutical companies in trials of new medications for over 15 years.

What is FerriSmart®?

FerriSmart® is a standardized, FDA cleared, MRI method for the measurement of LIC. FerriScan® and FerriSmart® are the only products to have FDA clearance as a companion diagnostic for use with deferasirox. FerriSmart uses artificial intelligence to perform automated analysis and provide instantaneous results by delivering a report back to the clinician and patient in real-time. FerriSmart was trained by FerriScan®. The accuracy and reliability of FerriScan® and FerriSmart® provide clinicians with data required to optimize patient treatment based on their actual level of liver iron overload.

How does FerriSmart® work?

FerriSmart® is a stand-alone software application that automatically analyses MRI (DICOM) images that are uploaded via the FerriSmart web portal. These images, acquirable on most makes and models of 1.5 Tesla MRI machines, are obtained through a unique and standardized scanning sequence to ensure results are accurate, reliable, and reproducible over time and between hospitals and the various makes and models of MRI scanners. Upon the automated analysis, a Liver Iron Concentration Report is delivered back to the MRI Centre (or Hospital) on-screen instantaneously

Due to the quality-controlled, standardized nature of the test, a patient may have a FerriSmart® at any FerriSmart-verified MRI centre, anywhere in the world, and receive accurate, reliable results.

How do I request a FerriSmart® from my doctor?

Ask your doctor if you need a FerriSmart® to measure your LIC and if there is a local radiology centre that offers the service. Further information can be obtained by contacting us at Resonance Health via info@resonancehealth.com.

Does FerriSmart® cause side effects?

No. MRI works using electro-magnetic energy, not radiation, so it is safe for people of all ages to have a FerriSmart® as often as required. There are some restrictions associated with MRI use, such as in pregnancy or in people who have metal implants, but these will be discussed with patients by the MRI technicians beforehand.

Is FerriSmart painful?

Being non-invasive, FerriSmart® is a painless test. Some people may experience anxiety in an MRI scanner as it can be noisy and can feel a little claustrophobic, however MRI technicians are very experienced at putting patients at their ease.

Is FerriSmart® approved by regulatory bodies? Can it be used anywhere in the world?

FerriSmart has the following regulatory clearances:

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

Who is the test suitable for?

FerriSmart® is suitable for patients of all ages. Because it is non-invasive, it is painless and can be used repeatedly. It does not require a contrast agent or a breath-hold. This means that very young patients who may require some sedation to keep still enough for an MRI scan can also successfully have a FerriSmart®.

Who should have this test?

People who have had serum ferritin tests that indicate they may have high levels of body iron, especially if they have:

- a disease that is likely to lead to iron overload
- repeated blood transfusions
- a genetic predisposition to absorb excessive amounts of iron.

How long does FerriSmart® take?

FerriSmart has a 7 to 10 minute scan time. Results are then analyzed and returned to the MRI Centre instantaneously upon the uploading of the DICOM (MRI) images to the FerriSmart web portal.

Do I need medicine before I take this test?

No medication is required before this test.



Validate Report

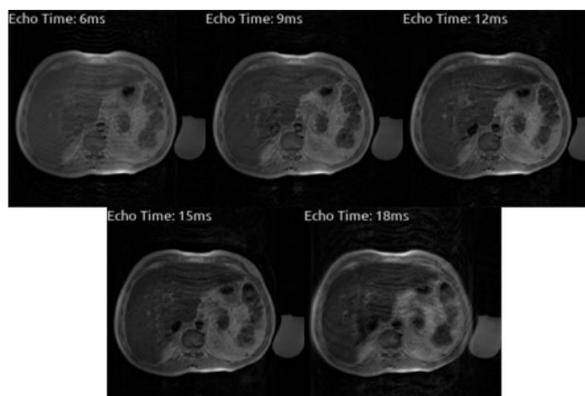
What does the FerriSmart® report look like?

- Patient information can be seen at the top of the report.
- In some countries, because FerriScan® is a very well-known test, sometimes patients may be told they have “had a FerriScan” as a general term to describe a liver MRI, however not all MRI-based tests are equal. The QR code (top right of report) provides patients and clinicians with a way to authenticate FerriSmart reports.
- Liver iron concentration results are displayed in the square box. In this report, the 3.5mg/g dry tissue indicates the average LIC of the patient. This 3.5 mg/g dry tissue and its clinical relevance can be seen in the table below.

Report No:	a85d16d386d4e925	Scan Date:	30 Aug 2017
Patient ID:	ABC-12345678	Analysis Date:	30 Nov 2018
Name:	PATIENT, Patient	Referrer:	Dr Doctor
Birth Date:	10 Aug 2003	MRI Center:	MRI Centre Name

Average Liver Iron Concentration:	
3.5 mg/g dry tissue	63 mmol/kg dry tissue
[95% CI: 3.0 - 4.1]	[95% CI: 53.5 - 74.3]
(NR: 0.17 - 1.8)	(NR: 3-33)

The 95% confidence intervals [95% CI] are derived from a study of repeat measurements by St Pierre et al., HemaSphere 2018;2: 188
 Normal range (NR) is taken from Bassett et al., Hepatology 1986;6: 24-29



What does my FerriSmart® result mean?

The below table shows the LIC thresholds in Transfusional Iron Overload, and their clinical relevance.

Extract from Olivieri et al, Blood 1997; 89, 739-61

LIC Range	Clinical Relevance
0.17-1.8 mg Fe/g dw	Normal range in non-disease patients in healthy population
3.2-7.0 mg Fe/g dw	Suggested optimal range of LIC for chelation therapy in transfusional iron loading
7.0-15.0 mg Fe/g dw	Increased risk of complications
>15.0 mg Fe/g dw	Greatly increased risk of cardiac disease and early death in patients with transfusional iron overload

How much does FerriSmart® cost?

The way in which FerriSmart® is charged varies between countries and even between centres, depending on the health funding available. As FerriSmart® consists of an MRI scan and subsequent analysis with FerriSmart software, some MRI centres will charge you for the test if funding is not available through local health arrangements.

Your clinician should be able to assist you to obtain information relevant to your local area.

Who is Resonance Health?

Resonance Health Limited is a publicly listed Australian healthcare company developing and delivering services to assist the non-invasive diagnosis and management of human disease.

Where can I find more information about FerriSmart®?

Visit our website at www.resonancehealth.com or contact us at info@resonancehealth.com.