

FerriScan[®] - R2-MRI Measurement of Liver Iron Concentration

FerriScan is an MRI-based solution for measuring liver iron concentration (LIC) in patients with iron overload. It provides a reliable measure of a patient's LIC to guide decisions on initiation and adjustment of chelation therapy.

FerriScan was cleared by the FDA for the measurement of LIC in 2005. In January 2013 FerriScan gained an additional clearance from the FDA as a companion diagnostic to aid in the identification and monitoring of non-transfusion-dependent thalassemia patients receiving therapy with deferasirox.

*"The liver iron concentration imaging companion diagnostic for deferasirox is essential to the safe and effective use of deferasirox in patients with non-transfusion-dependent thalassemia."*¹

FerriScan has been used extensively in multi-centre clinical trials for iron chelation therapies and in clinical practice since 2005. Currently used in more than 30 countries, over 25,000 FerriScan analyses have been performed.

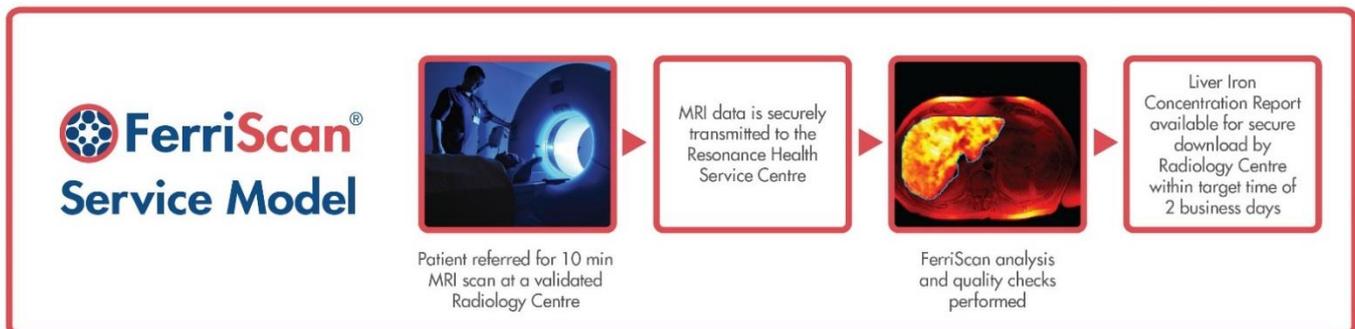
FerriScan was originally calibrated against liver biopsy in 105 patients with various iron overload conditions². A further multi-centre validation study on five different scanners with 233 patients concluded³:

- The FerriScan technique is robust;
- There is no shift in accuracy or precision between MRI scanners;
- FerriScan is unaffected by fibrosis or chelation therapy; and
- FerriScan can be used with patients of all ages

Following a ten-minute MRI scan, patient image data are transmitted electronically to Resonance Health's central image analysis facility over a secure network. A patented analysis method is applied to the liver images, providing a mean LIC value.

Key FerriScan Features

- ✓ FerriScan provides an accurate, validated MRI-based measurement of liver iron concentration
- ✓ FerriScan is non-invasive, requires no contrast agents and has a scan time of approximately 10 minutes
- ✓ FerriScan has high sensitivity and specificity for measuring LIC
- ✓ Image analysis and LIC reporting is performed at a central ISO 13485 certified Service Centre
- ✓ FerriScan has international regulatory clearance (USA, Europe, Australia)
- ✓ Results are available within a target time of two business days
- ✓ FerriScan can measure LIC over the entire range encountered in clinical practice³
- ✓ FerriScan results are clinically validated to be unaffected by inflammation, fibrosis or cirrhosis
- ✓ FerriScan requires no breath-hold and may therefore be used for paediatric patients
- ✓ Results are accurate, reliable and reproducible over time and between MRI centres and models of scanner
- ✓ There is no requirement for customers to purchase new software or hardware
- ✓ FerriScan is suitable for 1.5 Tesla MRI scanners
- ✓ FerriScan is charged per scan only



FerriScan Sensitivity and Specificity

LIC threshold (mg Fe/g dw)	Clinical relevance <i>(Taken from Olivieri and Brittenham, Blood 1997; 89:739-61)</i>	FerriScan R2-MRI	
		Sensitivity (95% confidence limits) %	Specificity (95% confidence limits) %
1.8	Upper 95% of normal	94% (86-97)	100% (88-100)
3.2	Suggested lower limit of optimal range for LICs for chelation therapy in transfusional iron loading	94% (85-98)	100% (91-100)
7.0	Suggested upper limit of optimal range for LICs for transfusional loading and threshold for increased risk of iron-induced complications	89% (79-95)	96% (86-99)
15	Threshold for greatly increased risk for cardiac disease and early death in patients with transfusional iron overload	85% (70-94)	92% (83-96)

Monitoring Iron Overload

Excess iron is deposited in tissues of the body, particularly the liver, eventually causing tissue damage and organ failure. For patients affected with iron overload, accurate monitoring of the body iron burden is crucial to the management of their disease. Liver iron concentration (LIC) provides the best measurement of total body iron stores, informing clinician decisions on initiation and adjustment of chelation therapy.

Effective control of total body iron stores has been shown to significantly reduce the risk of cardiac disease and early death in patients with thalassemia major.⁴

Serum Ferritin

Blood markers such as serum ferritin are confounded by factors other than iron loading, such as inflammation.

- Serum ferritin measurements are an unreliable predictor of iron loading in thalassemia major as they can be impacted by inflammation, infection and other conditions.⁵
- Serum ferritin has been found to significantly underestimate iron loading in thalassemia intermedia.⁶
- In HbE thalassemia, serum ferritin measurements have been shown to be of little clinical value in assessing body iron burden.⁷

FerriScan provides a reliable indication of total body iron on which to base decisions on chelator initiation and dose adjustment. An annual FerriScan is recommended to benchmark the patient's progress under chelation.

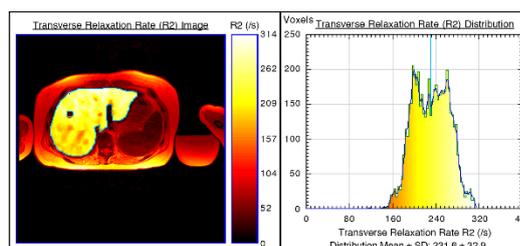
The FerriScan LIC Report

The FerriScan LIC Report provides the LIC result in mg / g dry tissue. The clinical relevance of this measurement can be assessed by means of a table provided in the report.

A map and a histogram indicating the distribution of iron throughout the liver is also featured in the FerriScan LIC report, providing further information on the patient's iron loading status.

Average Liver Iron Concentration	28.5 mg/g dry tissue	(NR: 0.17-1.8)
	510 mmol/kg dry tissue	(NR: 3-33)

Normal range (NR) is taken from Bassett et al., Hepatology 1986; 6: 24-29



References

1. http://www.accessdata.fda.gov/cdrh_docs/reviews/K124065.pdf
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3. St Pierre, T et al. Multicenter validation of Spin-Density Projection-Assisted R2-MRI for the Non-Invasive Measurement of Liver Iron Concentration. **Magnetic Resonance in Medicine** 2013; doi: 10.1002/mrm.24854.
4. Brittenham GM et al. Efficacy of Deferoxamine in Preventing Complications of Iron Overload in Patients with Thalassemia Major. **American Journal of Hematology** 42:81-85 (1993).
5. Olivieri NF et al Iron-chelating therapy and the treatment of thalassemia. **Blood** 1997; 89: 739-61.
6. Taher, A. et al. Correlation of liver iron concentration determined by R2 magnetic resonance imaging with serum ferritin in patients with thalassemia intermedia. **Haematologica**, 2008.93.1584-6.
7. St Pierre, T et al. Relationship Between Serum Ferritin and Liver Iron Concentration in Hemoglobin E Thalassemia. Abstract submitted for **European Hematology Association Congress** 2011.