



THE UNIVERSITY OF
**WESTERN
AUSTRALIA**



MRI diagnostics of iron overload using the affordable, AI-trained method FerriSmart

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The University of Western Australia

Webinar 28th September 2023



ARISE

African Research And Innovative
Initiative For Sickle Cell Education

Competing interests

- I have part time employment with Resonance Health Analysis Services Pty Ltd (the providers of FerriScan[®], FerriSmart[®], and LiverSmart[®])

Who am I?

- I am a physicist by training.
- I live and work in Australia.
- My research career has focused on measuring the properties and quantities of iron in biological tissues.
- I have worked with many medical practitioners on applications of magnetic resonance imaging to the measurement of iron concentrations in the human body.
- I have a strong interest in sickle cell disease and thalassaemia.

Previous Webinar

- Basics of iron metabolism;
- Causes of iron overload;
- The need for measurement of liver iron concentration;
- Introduction to measurement of LIC.

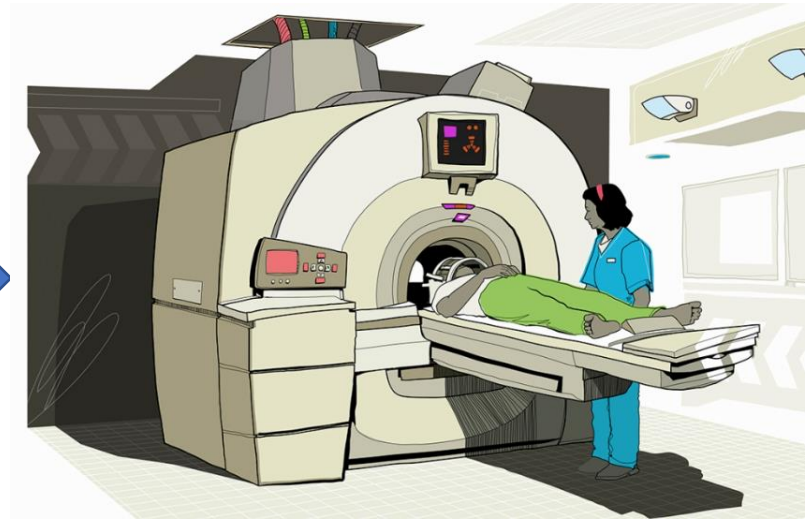
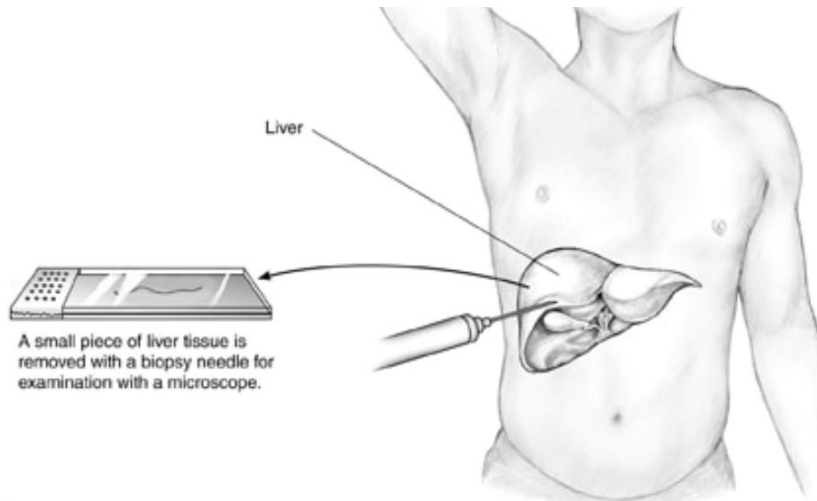
This webinar

- Introduction to principles of tissue iron measurement by MRI;
- Introduction of the FerriScan MRI technique for measuring LIC;
- Evidence for the diagnostic accuracy of FerriScan;
- Introduction to the automated FerriSmart MRI method for LIC;
- Evidence for diagnostic accuracy of FerriSmart;
- How to get started.

Measurement of Liver Iron Concentration in Transfused Patients

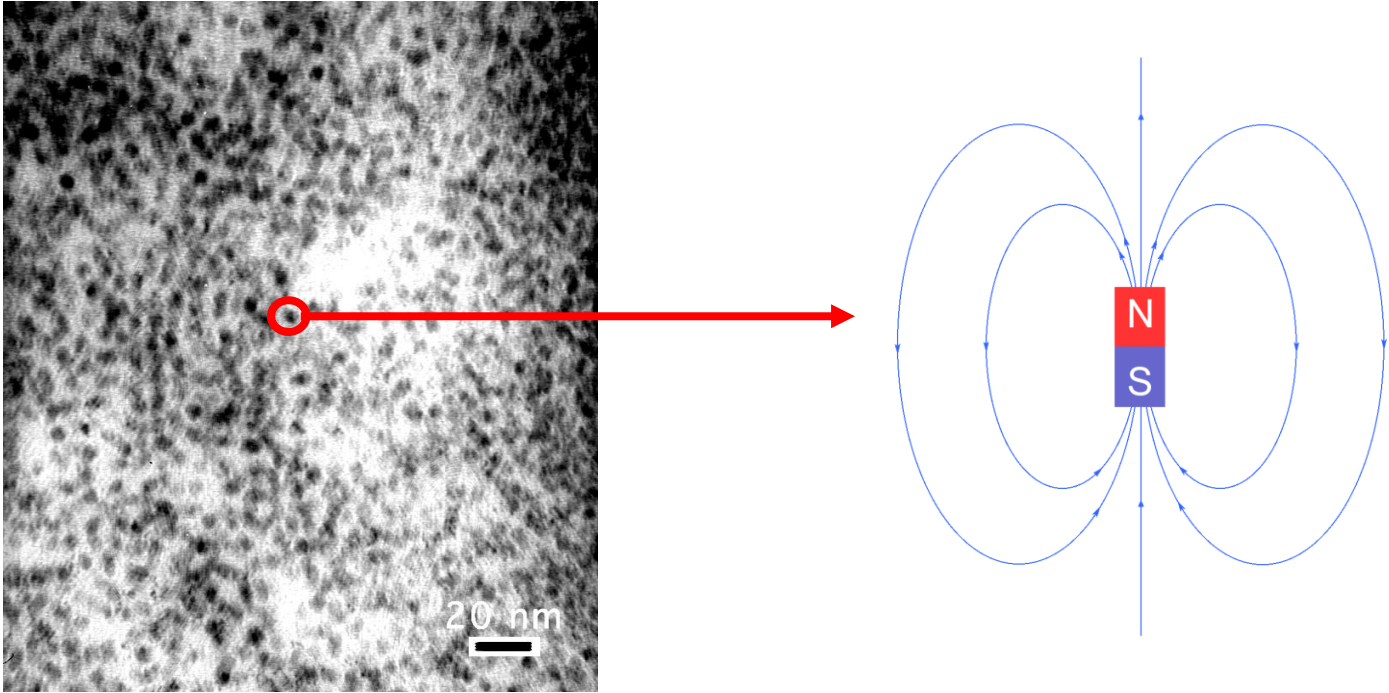
- Liver iron concentration (LIC) is used as an indicator of total body iron stores
- Accurate measurements are required to aid hematologists on decisions on when to
 - Initiate or cease iron chelation therapy
 - Increase iron chelation dose
 - Decrease iron chelation dose
 - Alter chelator or mode of delivery of chelator
- Ineffective chelation therapy leads to organ damage and increases the risk of early death

MRI has largely replaced biopsy for LIC measurements



How can we use MRI to measure the concentration of iron in the liver?

In a magnetic field, the rust particles in the liver become small magnets!



Transmission electron microscope image of iron loaded liver

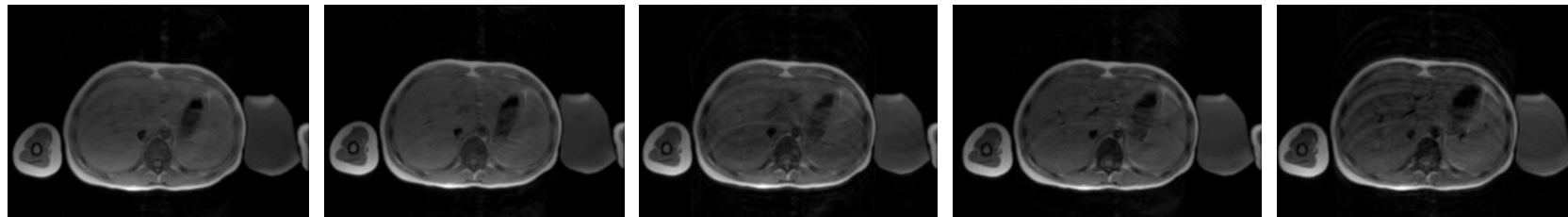
6 ms

9 ms

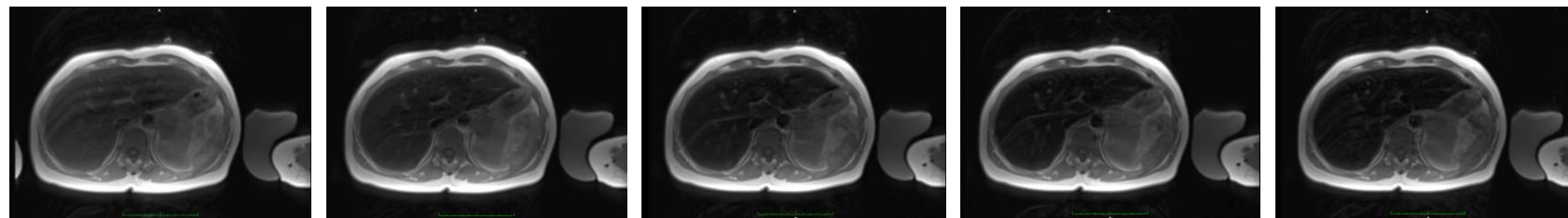
12 ms

15 ms

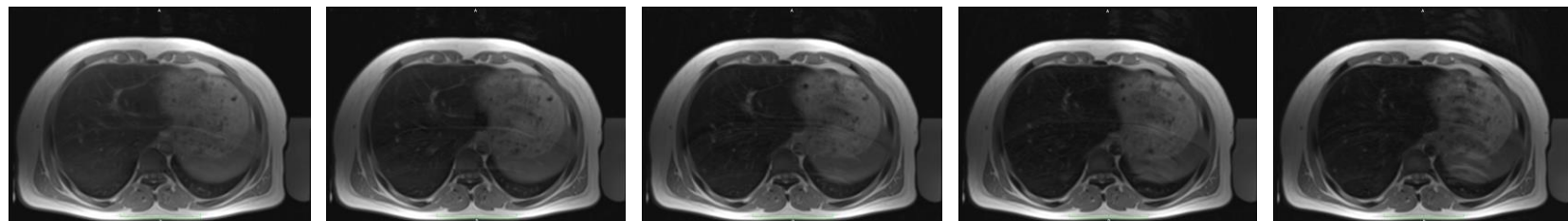
18 ms



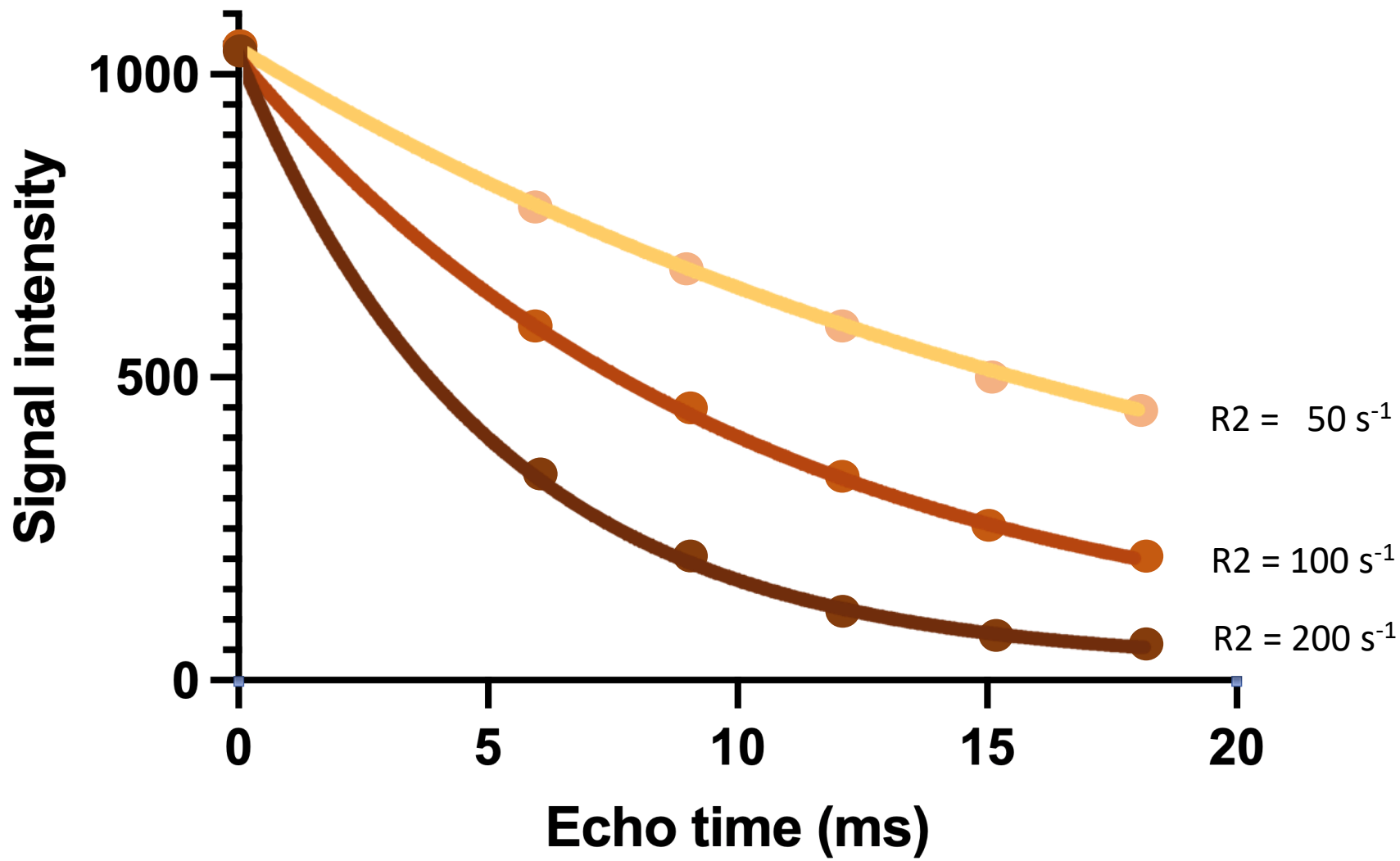
LIC = 1.9 mg Fe/g dw R2= 50 s⁻¹



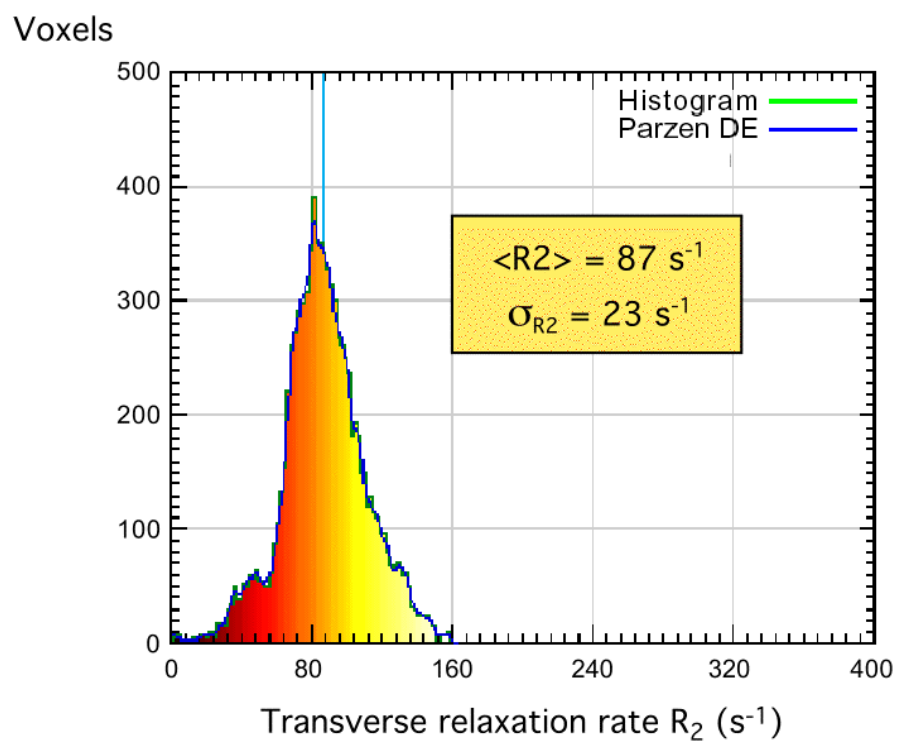
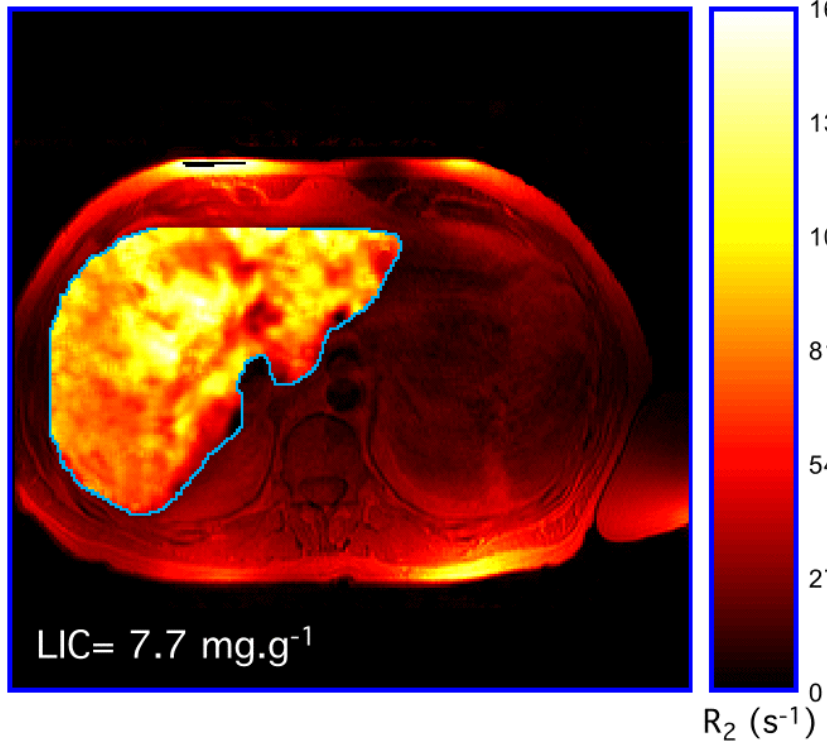
LIC = 6.3 mg Fe/g dw R2= 100 s⁻¹



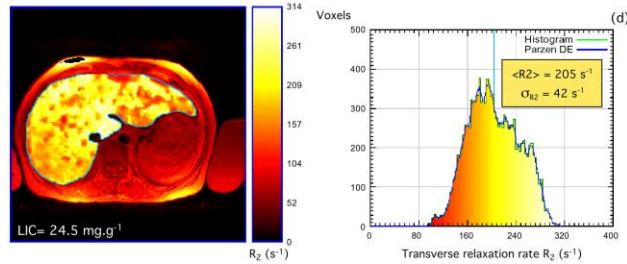
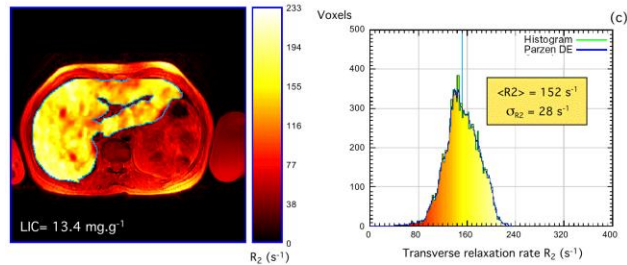
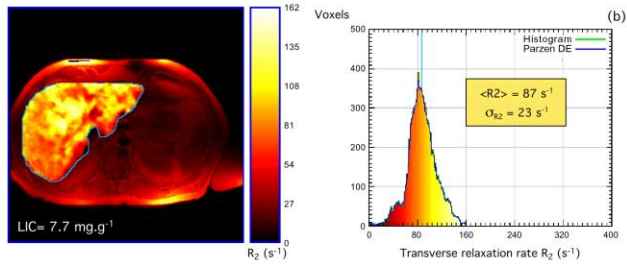
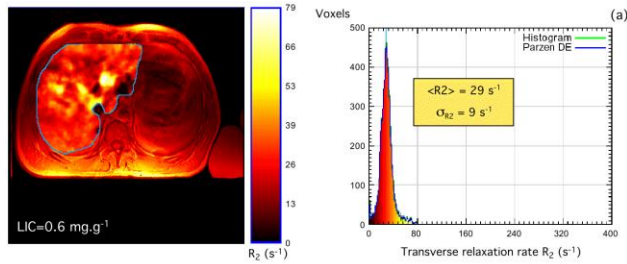
LIC = 21.2 mg Fe/g dw R2 = 200 s⁻¹



FerriScan[®] - a way of using MRI to evaluate the concentration of rust particles in liver



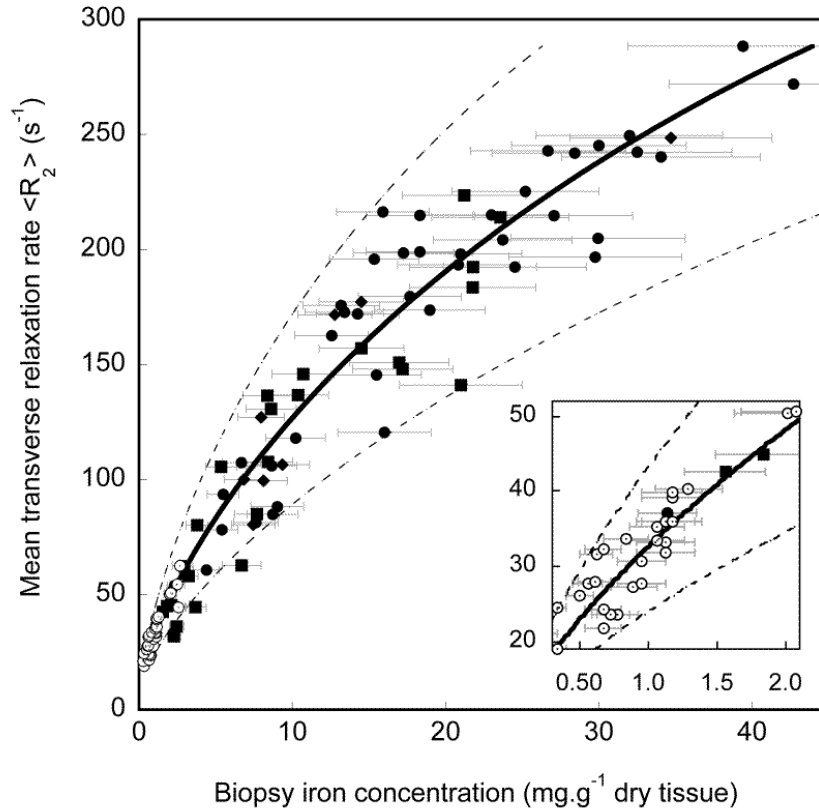
FerriScan[®]



Normal iron

Very high iron

Relationship between FerriScan[®] measured liver R2 and needle biopsy LIC (dry weight)



- 105 subjects
- LIC measured from biopsy
- Data from 5 different scanners
- Patients with
 - Thalassemia major
 - Thalassemia intermedia
 - Hereditary hemochromatosis
 - Non-iron loading liver disease

Horizontal error bars represent the standard error on biopsy measurement of LIC

How does FerriScan[®] work?

- FerriScan[®] is based on the measurement of the proton transverse relaxation rate R_2 (or $1/T_2$) using MR scanners.
- A series of single spin echoes is acquired.
- A patented spin-density-projection method is used to enable very high relaxation rates associated with severe iron overload to be measured.
- Measurement of R_2 rather than R_2^* avoids confounding effects of fat.

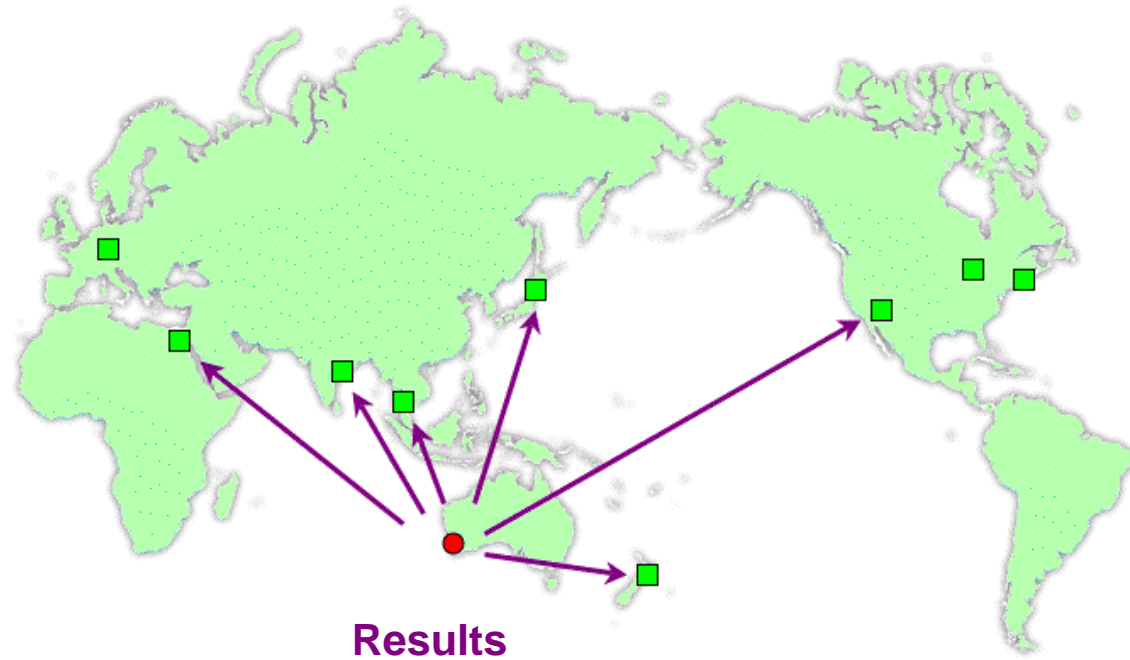
How does FerriScan[®] work?

- Free breathing protocol enables measurement of patients who may have difficulty with breath holding (sedated children or frail patients).
- FerriScan[®] uses a patented data analysis method to account for breathing artefacts manifested in images.
- The value of liver R2 measured using FerriScan[®] is converted to a LIC value via a calibration that has been developed and subsequently validated on multiple makes and models of 1.5T scanners (and more recently 3T scanners).

How does FerriScan[®] work?

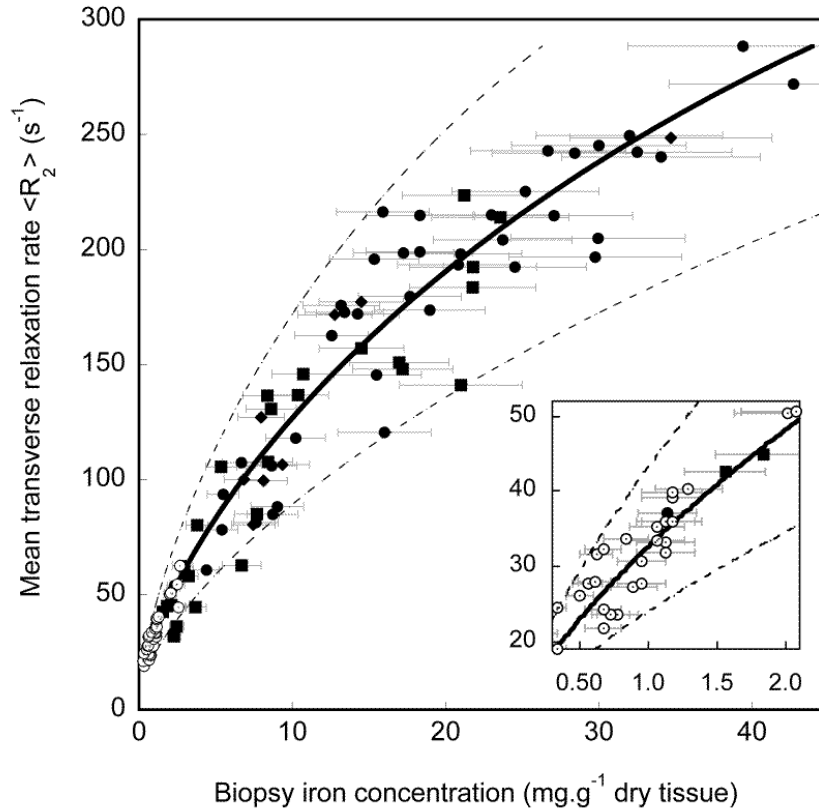
- FerriScan[®] data acquired on a scanner are transmitted through a secure link to a core lab for
 - Input data quality control
 - Data analysis under quality assured system
 - Preparation of LIC report

FerriScan[®] - data analysis procedure



FerriScan[®] Calibration & Validation

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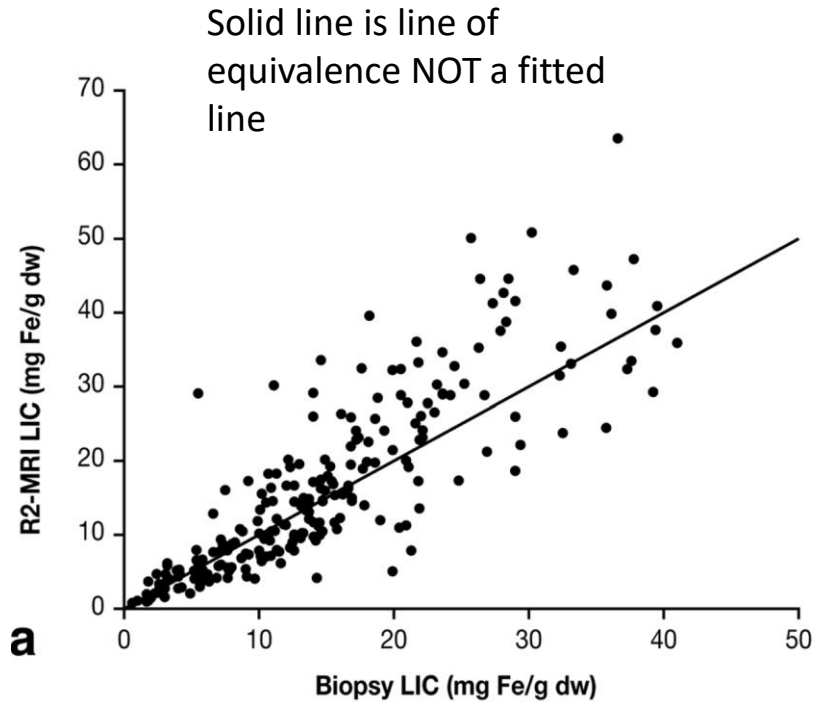
Horizontal error bars represent the standard error on biopsy measurement of LIC

FerriScan[®] Sensitivity & Specificity

LIC threshold (mg Fe/g dry weight)	Clinical Relevance	FerriScan [®] Sensitivity (95% CI)	FerriScan [®] Specificity (95% CI)
1.8	Upper 95% of normal	0.94 (0.86-0.97)	1.00 (0.88-1.00)
3.2	Suggested lower limit of optimal range for LICs for chelation therapy in transfusional iron loading	0.94 (0.85-0.98)	1.00 (0.91-1.00)
7.0	Suggested upper limit of optimal range for LICs for transfusional iron loading and threshold for increased risk of iron-induced complications	0.89 (0.79-0.95)	0.96 (0.86-0.99)
15.0	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)

The risks associated with each LIC threshold are taken from **Olivieri and Brittenham, *Blood* 1997: 89, 739-61**. The sensitivity and specificity of FerriScan[®] measurements for discrimination of needle biopsy iron assay values above the clinically important LIC thresholds are taken from **St Pierre et al. *Blood* 2005: 105, 855-61**.

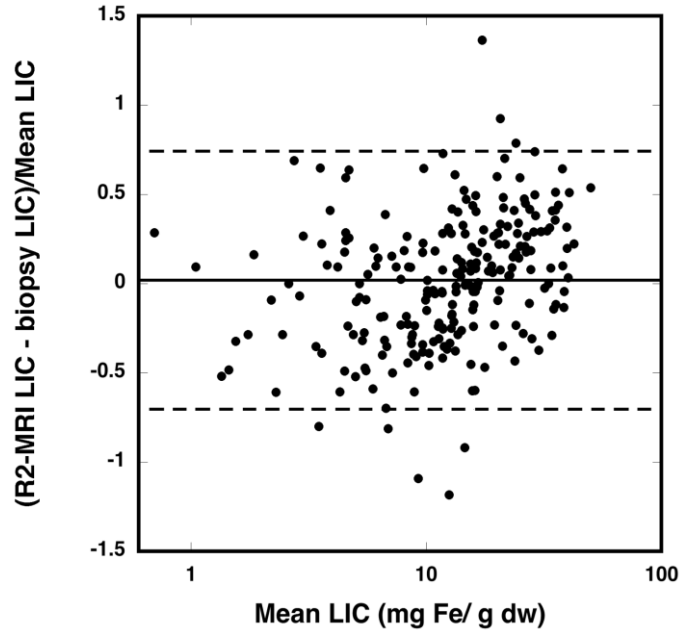
Validation of Calibration



No statistically significant shift in calibration observed

- 233 additional thalassemia major subjects
 - ESCALATOR study (Novartis)
- 5 different scanner models
- Age range 3 to 43 years
- All regularly transfused
- All chelated with deferasirox for 12 months
- All subjects had LIC measured by biopsy
- MRI analysts blinded to biopsy results

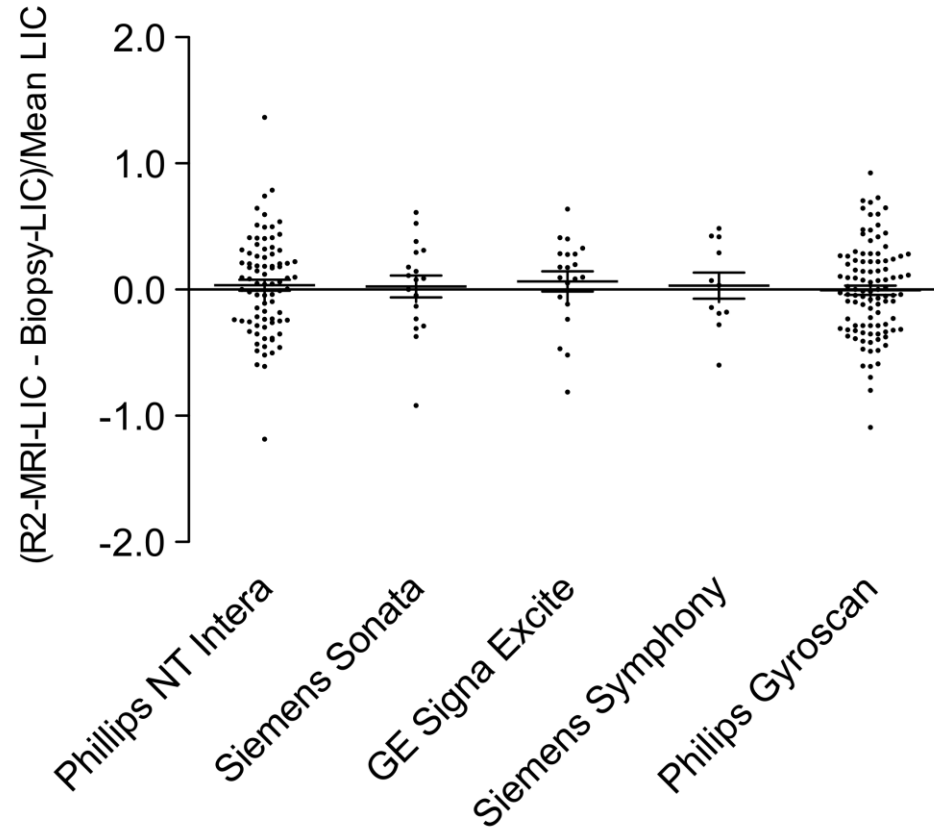
Validation of Calibration



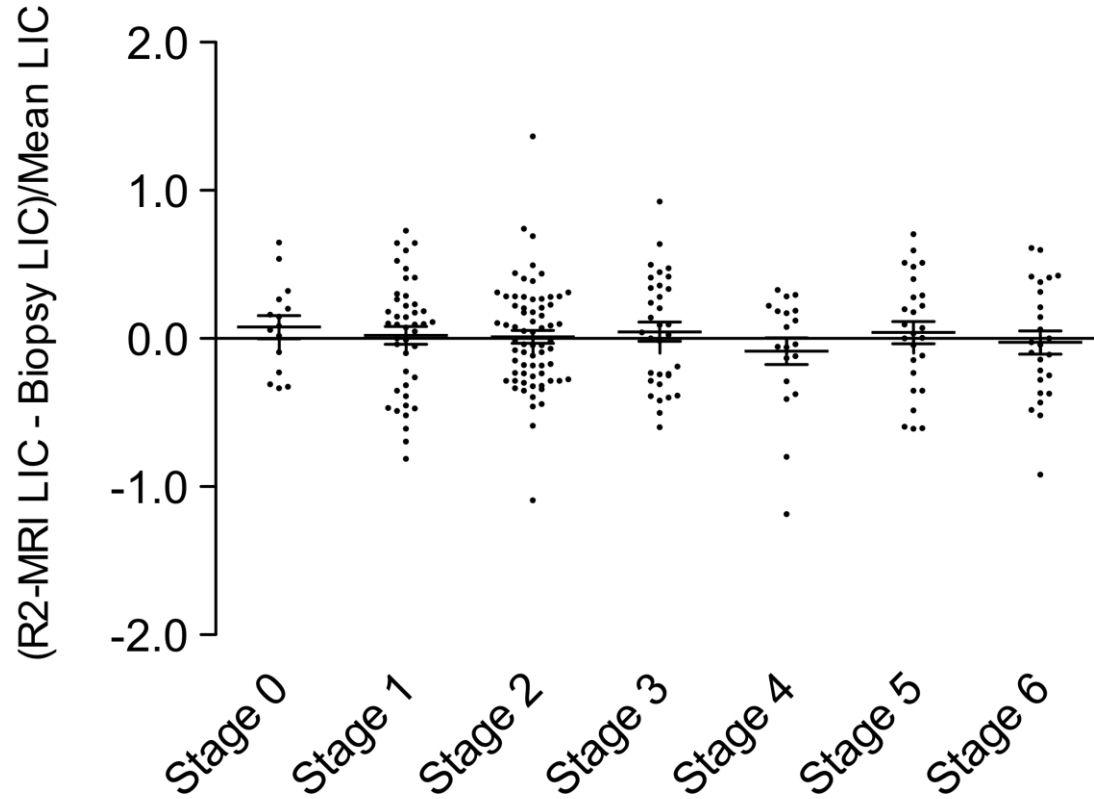
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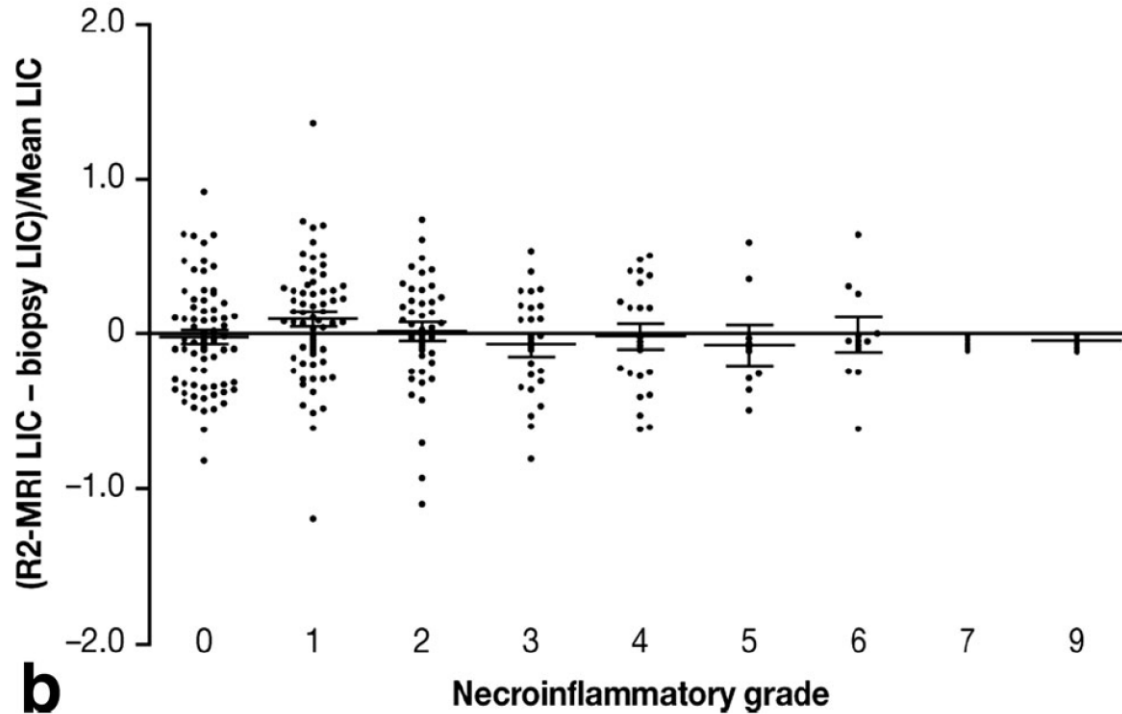
FerriScan[®] calibration stable across scanner makes and models



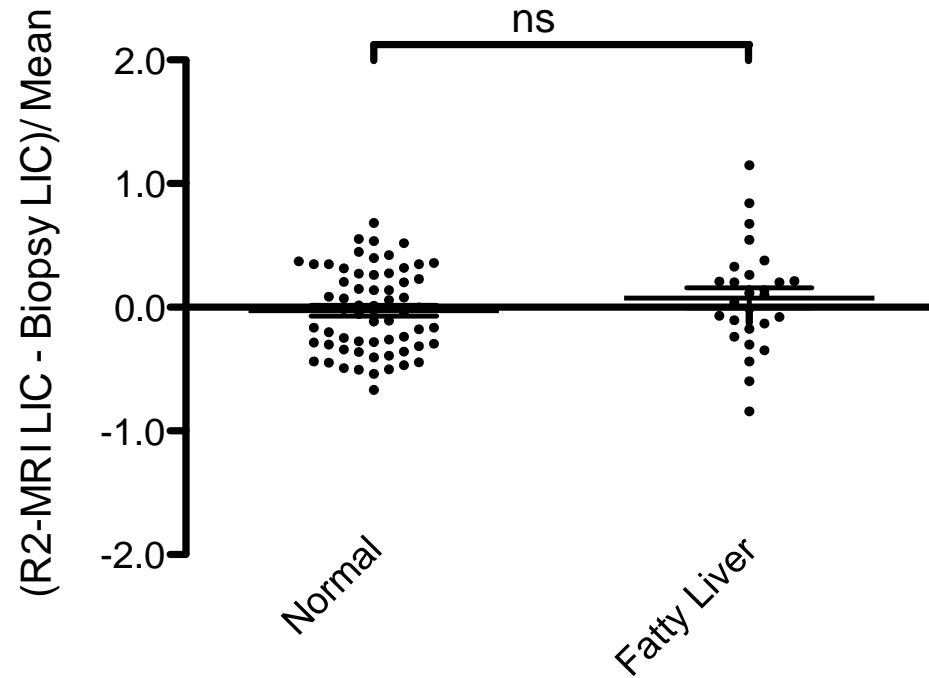
FerriScan[®] Calibration Stable Across Liver Fibrosis Stages



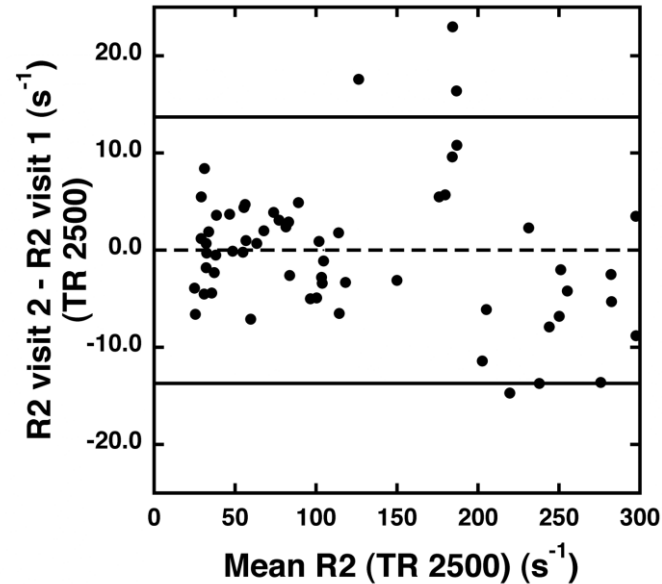
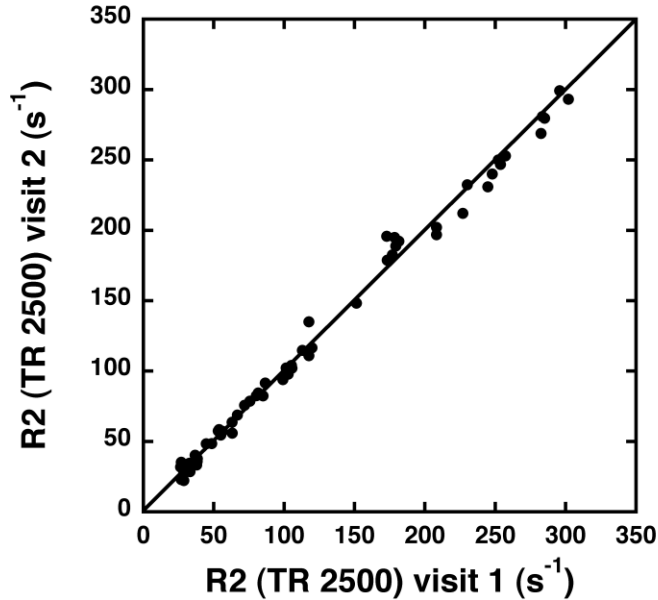
FerriScan[®] Calibration Stable Across Grades of Liver Necroinflammation



FerriScan[®] Calibration Stable in Presence of Fatty Liver



Repeatability of liver R2 measurements by FerriScan[®]



**Corresponds to standard error on LIC of approx 15%
(better than biopsy)**

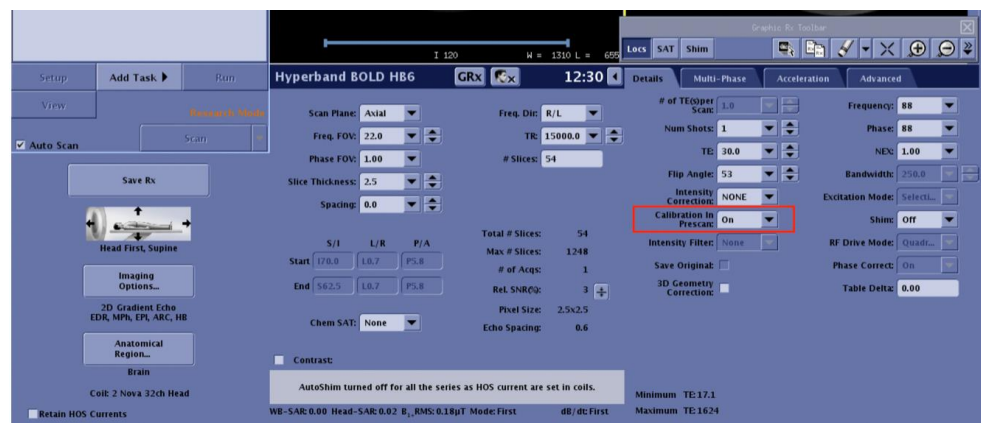
Points to note about FerriScan

- Has high sensitivities and specificities for predicting LIC by biopsy;
- Has been validated on multiple makes and models of 1.5T scanners;
- Is not confounded by the presence of fibrosis, inflammation or fat;
- Has a high degree of repeatability;
- Can be used on very young children and adults;
- Requires transmission of image data to a central laboratory for processing.

Is non-invasive measurement of liver iron by
MRI widely available?

Challenges to widespread use of liver iron measurement by MRI

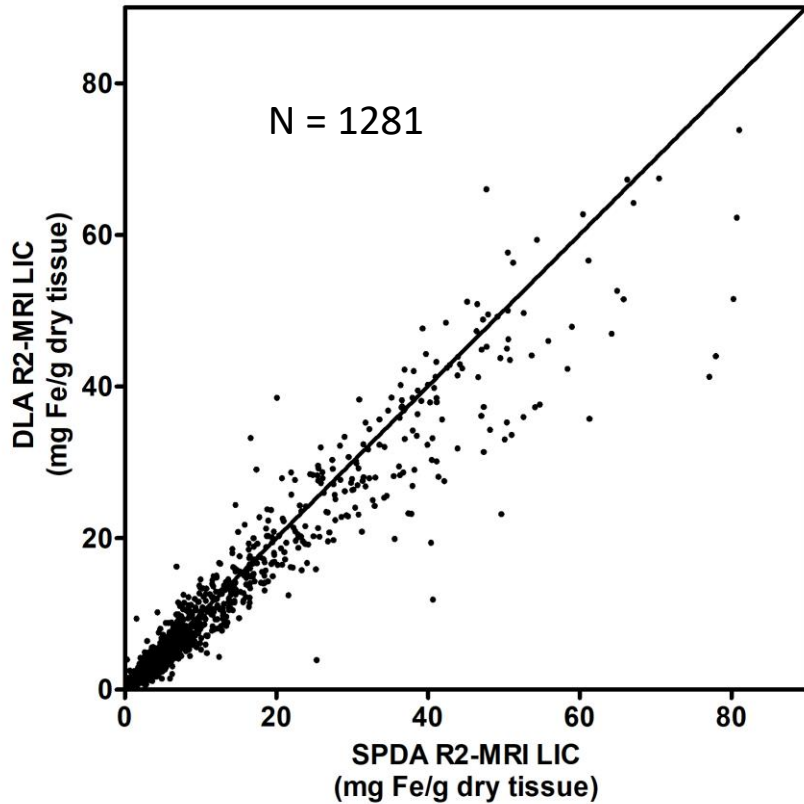
- Expertise/training of radiographers and radiologists required
 - Quality control of acquired image data
 - Image data analysis
- Outsourcing of quality control & data analysis available
 - Delay in receiving results
 - Higher costs associated



A new artificial intelligence trained data analysis system (FerriSmart®)

- The new DLA R2-MRI system (FerriSmart)
 - Is a fully automated data analysis system for LIC evaluation by MRI (drag and drop data analysis);
 - It uses a data acquisition technique identical to FerriScan (which has been shown to be achievable even on very old 1.5T scanners);
 - Checks that image data have been acquired correctly;
 - Gives immediate feedback to radiographers/radiologists on data acquisition errors;
 - Does NOT give a LIC result if data have been acquired incorrectly;
 - Provides a liver iron concentration report within seconds of uploading correctly acquired image data (by using trained convolutional neural networks);
 - Has regulatory approval from the FDA and CE Mark in Europe.

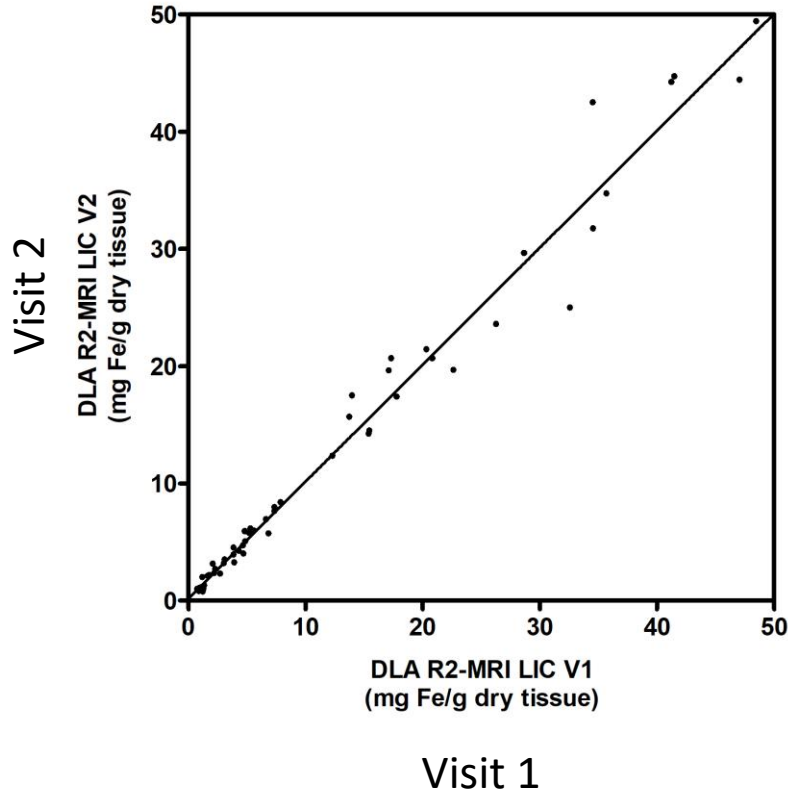
Diagnostic performance of FerriSmart®



Clinically relevant threshold (mg Fe/g dry tissue)	Sensitivity [95% CI] (%)	Specificity [95% CI] (%)
3.0	96 [94-97]	95 [92-98]
5.0	91 [89-94]	97 [95-99]
7.0	92 [90-95]	97 [95-98]
15.0	89 [85-93]	98 [98-99]

Geometric mean ratio of FerriSmart to FerriScan LIC is 0.93 (95% CI 0.92 - 0.95) above 3 mg Fe/g dry tissue

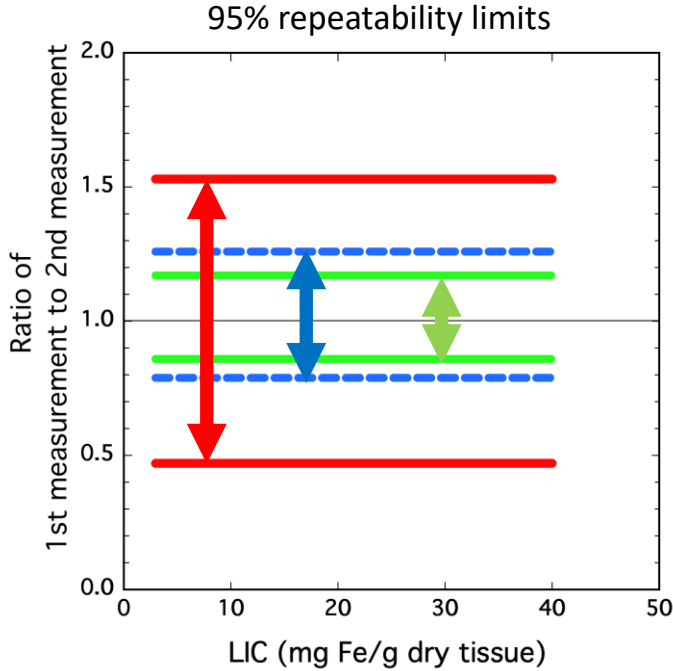
Repeatability of FerriSmart®



- 50 patients and 10 healthy controls
- Each measured twice with DLA R2-MRI
- Time between visits: min:1 hour max:7 days
- 95% of the repeat measures of LIC by DLA R2-MRI had ratios that fall between 0.79 and 1.26 **above 3 mg Fe/g dw**
- 95% of the repeat measures of LIC by DLA R2-MRI had ratios that fall between 0.64 and 1.57 **below 3 mg Fe/g dry tissue.**

Comparative repeatability

(above 3mg Fe/g dry tissue)



Biopsy – best case scenario (no liver disease)*

Reference standard (FerriScan)

New FerriSmart method (DLA R2-MRI)

1. *Emond, et al. (1999) Clinical Chemistry, 45: 340.
2. *Kreeftenberg, et al. (1984) Clinica Chimica Acta., 144: 255.

Is it difficult to process the MRI images to obtain a Liver Iron Concentration report?



DR TIM ST PIERRE, RHAS R&D

New Patient Job - Select Service

- HOME |
- NEW PATIENT JOB** |
- REFERRING CLINICIANS |
- PHANTOM SCAN |
- JOB LIST |
- ACCOUNT DETAILS |
- UNIQUE DEVICE IDENTIFIER |

- LOGOUT |

Please select a Service for a New Patient Job

- FerriSmart
- HepaFat-AI

Summary and Conclusions

- The new AI based FerriSmart system provides automatic data quality control to minimise probability of problematic measurements of LIC and give feedback to radiologists.
- The new AI based FerriSmart system automatically produces a liver iron concentration report from the MRI data.
- The repeatability of the FerriSmart method for LIC measurement is significantly better than that for liver biopsy methods.
- While there is an overall bias between the FerriSmart and the reference standard SDPA R2-MRI (FerriScan), the bias does not result in unacceptable sensitivities and specificities of FerriSmart for predicting SDPA R2-MRI (FerriScan) results above the clinically relevant LIC thresholds.
- The bias between the automated and manual methods indicates that the two techniques should not be used interchangeably.

What is it like for a patient to have a FerriSmart scan?

- The procedure is completely **non-invasive**.
- **No injections** or contrast agents are required.
- The patient lies down on a bed and has a “radio-antenna” placed on their abdomen.
- Patient will be given **earmuffs or headphones** to protect ears from loud noises.
- The radiographer will then slide patient into the tube of the scanner.
- A few minutes are spent by the radiographer adjusting the settings of the scanner.
- The FerriSmart images are the acquired over about **10 minutes** during which the patient is asked to lie still and breathe gently.
- The patient will hear some **rhythmic knocking noises** during the scan.

How do I get started with FerriSmart?

- As part of this ARISE training project, we aim to help teams in Africa implement LIC measurement by MRI.
- For radiology/haematology teams in Africa, email:

stephanieM@resonancehealth.com

- Stephanie will guide you through the process of setup:
 - How to register your MRI scanner for FerriSmart;
 - Instructions for setting up the image acquisition protocol;
 - Real time assistance with your very first scan;
 - Setting up account and passwords to access the FerriSmart portal.

Further information

- For further information on measurement of tissue iron by MRI

Tim St Pierre <Tim.StPierre@uwa.edu.au>

- For further information on haemoglobinopathies

Inusa Baba <Baba.Inusa@gstt.nhs.uk>



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AUSTRALIA**



Thank you for joining the webinar today

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