FerriScan®

MRI Measurement of Liver Iron Concentration

Guidelines Supporting the Use of FerriScan R2-MRI to Measure Liver Iron Concentration

Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, 2016

UK Forum on Haemoglobin Disorders in association with the UK Thalassaemia Society

"Liver Iron Concentration LIC should be assessed using a validated and standardised MR technique. R2 (FerriScan) is preferable to R2 because the methodology is more robustly standardised and has been licensed for use in routine clinical practice."*

"MRI LIC methods should not be used interchangeably. In particular, sequential MRI estimations in an individual patient should be done with the same methodology."

Guidelines for the Standard Monitoring of Patients with Thalassemia: Report of the Thalassemia Longitudinal Cohort, 2015

Tubman, VN, et al. Journal of Pediatric Hematology/Oncology, 2015. 37(3): p. e162-e169

"The LIC is usually monitored annually, and this practice led to changes in chelation after 40% of MRI studies. More frequent assessments (every 6 months) may be considered when the iron burden is high and intensive chelation is utilized. Conversely, if the LIC and ferritin are well controlled, monitoring the LIC every 18 to 24 months may be acceptable. Until recently, the gold standard for measuring LIC had been liver biopsy with quantification of liver iron by weight. The frequency of liver biopsy in the TCRN decreased significantly as R2- and T2-based MRI sequences have improved. Such MRI techniques have been validated to provide liver iron estimates that are equivalent to liver biopsy. Increased use of MRI has likely increased adherence to monitoring recommendations due to decreased morbidity of MRI compared to biopsy."*

Association of the Scientific Medical Societies in Germany, Guideline for diagnosis and treatment of secondary iron overload in patients with congenital anemias, 2015

"FerriScan is recommended to clinicians in Germany for the management of congenital anemias such as Sickle Cell Disease."

Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) 3rd Edition, 2014

Thalassaemia International Federation

"A note of caution is that the different MRI techniques may not be equivalent – at least in the manner they are currently calibrated and practiced."

"The R2 based FerriScan technique appears to have acceptable linearity and reproducibility up to LIC values of about 30 mg/g dry wt (St Pierre 2005), with an average sensitivity of >85% and specificity of >92% up to an LIC of 15 mg/g dry wt, and has been registered in the EU and US. For calibration of FerriScan, the MRI machine must use a Phantom supplied by the company, while the data acquired is sent via internet for analysis by dedicated FerriScan software (payment per scan analyzed). A particular advantage of this technique is that it can be applied with little training, at any centre with a reasonably up-to-date MRI machine."

News Release – January 2013

U.S. Food and Drug Administration

FDA approve FerriScan as first imaging companion diagnostic for chelation therapy.

"The FDA reviewed data for the FerriScan through the de novo classification process. The FDA's granting of the de novo request for FerriScan was based largely on data from the Exjade clinical studies that used FerriScan LIC results as the primary outcome measure. Additionally, investigators conducted a 230-patient study that found FerriScan results were as accurate as liver biopsy for measuring LIC."

"The FerriScan device is a non-invasive test that helps physicians to select appropriate patients for Exjade therapy as well as monitor their response to the drug, and discontinue therapy when LIC reaches safe levels."

Management of Beta Thalassaemia in Pregnancy Green-Top Guideline no. 66. 2014.

Royal College of Obstetricians and Gynaecologists (UK)

"Women should be assessed for liver iron concentration using a FerriScan® or liver T2. Ideally the liver iron should be < 7 mg/g (dry weight) (dw)."*

www.resonancehealth.com info@resonancehealth.com +61 8 9286 5300

Evidence-based Management of Sickle Cell Disease, Expert Panel Review, 2014

US Department of Health and Human Services

"In patients who receive chronic transfusion therapy, perform serial assessment of iron overload to include validated liver iron quantification methods such as liver biopsy, or MRI R2 or MRI T2 and R2* techniques. The optimal frequency of assessment has not been established and will be based in part on the individual patient's characteristics. (Strong Recommendation, Moderate-Quality Evidence)"*

Thalassemia Standards of Care Guideline, 2012

The Northern California Comprehensive Thalassemia Network and Children's Hospital, Oakland

"The Use of Imaging to Monitor iron Overload and Chelation Therapy. LIC is one way to determine total body iron content. While liver biopsy determination of LIC has been recommended for years, recent progress with MRI imaging provides an expedient and non-invasive way to directly measure LIC…"

"A FerriScan is a commercially available and validated system for quantitative MRI measurements of iron."

Guidelines for the clinical management of Thalassaemia, 2008

Thalassemia International Federation (TIF)

"LIC can also now be measured using MRI techniques, previously limited to a relatively narrow linear range. One recently described approach, is the R2 or FerriScan technique which appears to have acceptable linearity and reproducibility over the range of clinical interest (St Pierre TG, et al, 2005). The technique demonstrates an average sensitivity of >85% and specificity of >92% up to an LIC of 15 mg/g dry wt, and has been registered in the EU and US. For calibration, the MRI machine must use a Phantom supplied by the company, while the data acquired is sent via internet for analysis by dedicated FerriScan software (payment per scan analysed). A particular advantage of this technique is that it can be applied with little training, at any centre with a reasonably up-to-date MRI machine."

Iron overload in myelodysplastic syndromes: a Canadian consensus guideline, 2008

Wells and Colleagues

"The most accurate and precise MRI technique for measurement of LIC was developed by St. Pierre et al., who found mean liver proton relaxation rates (R2) correlated strongly with LIC, as determined by biopsy across a broad range of LIC values."

Australian guidelines for the assessment of iron overload and iron chelation in transfusion-dependent thalassaemia major, sickle cell disease and other congenital anaemias, 2011

Ho PJ, Tay L, Lindeman R, Catley L, Bowden DK.

"The quantitation of liver iron by MRI is one of the most significant recent advances in iron monitoring. The most widely adopted method is based on the measurement of tissue proton transverse relaxation rates (R2), showing excellent correlation with liver iron concentration (LIC) measured by biopsy.

Algorithms predicting risk of complications from liver biopsy LICs have been applied to LICs obtained by MRI, and hepatic iron remains the best measure of total body iron loading."

"The expert panel considers it to be a very useful method of monitoring liver iron load and in directing iron chelation therapy. An appropriate monitoring strategy would comprise annual R2 MRI for the majority, while this can be extended to every 2 years for patients with normal LIC or at the lower end of the ideal range (e.g. 3 – 5 mg/g dry weight) when there has been no change to chelator regimen, and perhaps increased to every 6 months in at-risk patients, such as those with LIC above 15 mg/g dry weight. LIC results should also be correlated with standard liver function tests."

The "Standards for the clinical care of adults with sickle cell disease in the UK", 2008

UK Sickle Cell Society

"All patients who have been previously transfused or are currently undergoing regular transfusions, whether top-up or exchange, should have regular quantitative monitoring of liver iron concentration using MRI".

"The quantitation of liver iron by MRI is one of the most significant recent advances in iron monitoring. The most widely adopted method is based on the measurement of tissue proton transverse relaxation rates (R2), showing excellent correlation with liver iron concentration (LIC) measured by biopsy. Algorithms predicting risk of complications from liver biopsy LICs have been applied to LICs obtained by MRI, and hepatic iron remains the best measure of total body iron loading."

Diamond Blackfan Anemia Chelation Therapy Fact Sheet, 2012

Diamond Blackfan Anemia Foundation, Inc

"FerriScan MRI is a special scan that shows the amount of iron in the liver. These tests are very accurate and are non-invasive, meaning that they do not require a blood test or insertion of a needle into the organ."

ASH Education Program Book, Consequences and management of iron overload in sickle cell disease, 2013

Porter, J and M Garbowski. 2013(1): p. 447-456.

"Value of LIC monitoring - The inconvenience, discomfort, and potential complications of liver biopsy can be avoided using MRI techniques.

A standardized and validated MRI method is now registered in Europe and the United States (FerriScan), with reproducible relationship between the value (R2) by MRI and LIC by biopsy over a clinically useful range in which locally acquired data are analyzed at a central facility. This is potentially available in any hospital with an MRI scanner and with minimal training of local staff."

Position Statement on MRI-Based hepatic Iron Assessment Methods, 2012

Cooley's Anemia Foundation

"The Cooley's Anemia Foundation strongly supports the consensus recommendations of the Thalassemia Clinical Research Network (TCRN) to obtain at least annual MRI for hepatic iron and cardiac iron T2 MRI beginning at age 10 years (with more frequent measurements considered for patients with cardiac T2* <10-20 ms) and an annual liver iron measurement, without a specified starting age, for transfusion-dependent patients and to adjust chelation in response to these measurements. We recommend that hepatic MRI methods be available to patients with thalassemia and other iron overload disorders. FerriScan® R2 is an FDA approved, MRI-based proprietary data analysis method capable of accurately measuring liver iron concentrations in patients regardless of the amount of iron in their liver, a feature particularly important for thalassemia patients with heavy iron loading."*

Guidelines for the Care of Patients in the UHN Red Blood Cells Disorders Program, 2012

University Health Network, Toronto General Hospital, Canada

"R2-MRI (FerriScan®) appears to be the most accurate non-invasive measure of hepatic iron loading."

"MRI is the primary tool used to monitor and make decisions regarding change in chelator dose or strategy."

"Liver MRI (R2, FerriScan) should be performed annually, except:

- *6 monthly – recent change in chelator*
- *18 months- 2 yearly - LIC<3 with continued good compliance"*

The Nursing Practice Guideline: Care of the patients with sickle cell disease and iron overload, 2008

International Association of Sickle Cell Nurses and Physician Assistants

"Effective management of iron overload begins with frequent assessment of iron burden. Ideally this should be a quantitative method of iron measurement which is safe, effective and provides a high level of accuracy." It lists FerriScan as achieving these criteria and thus is a suitable method for measuring LIC."

Italian Society of Hematology practice guidelines for the management of iron overload in thalassaemia major and related disorders, 2008

Angelucci E et al.

"The best result was obtained with the R2 methodology which resulted in a curvilinear relationship between R2 and LIC by biopsy over the entire clinically relevant range of LICs."

Long-term follow-up after hematopoietic stem cell transplant general guidelines for referring physicians (April 2013)

The Fred Hutchinson Cancer Research Center / Seattle Cancer Care Alliance

"While measurement of liver iron concentration is the gold standard, an iron-specific magnetic resonance imaging test (FerriScan) is highly accurate in measuring liver iron and is an alternative to liver biopsy for the measurement of hepatic iron content."

Clinical management of myelodysplastic syndromes: update of SIE, SIES, GITMO practice guidelines, 2010

Santini V et al

"Body iron content cannot be adequately assessed by serum ferritin, since inflammation and liver disease disproportionately elevate this circulating protein. Transferrin saturation is also of no value, since an isolated reticuloendotelial iron overload is associated with a normal saturation. According to SIE practice guidelines for the management of iron overload in thalassemic syndromes[1], the recommended non-invasive quantitative techniques to assess hepatic and cardiac iron content are R2 MRI and T2*MRI, respectively."

1 Angelucci E, Barosi G, Camaschella C, et al. Italian Society haematology practice guidelines for the management of iron overload in thalassemia major and related disorders. Haematologica 2008;93:741–52.

EASL Practice Guidelines for Hereditary Haemochromatosis[1]

"Many algorithms have been proposed for the diagnosis of HH. ***The EASL Clinical Practice Guidelines for HH recommend the following****:*

- *Patients with suspected iron overload should first receive measurement of fasting transferrin saturation (TS) and serum ferritin (SF)*
- *If transferrin saturation is increased, HFE testing for C282Y and H63D polymorphisms should be performed*
- *Diagnosis of HFE-haemochromatosis should not be based on C282Y homozygosity alone, but requires evidence of increased iron stores*
- *Direct assessment of liver iron stores in patients who have elevated SF concentrations and/or transferrin saturation should be performed. This approach is supported by the Dutch Guidelines for the diagnosis and treatment of HH[2] and publications by Camaschella[3], Gan et al[4] and Swinkels et al[5]"*

The European Association for the Study of the Liver Disease (EASL) Clinical Practice Guidelines for HFE Haemochromatosis[1] published in 2010 state that

"serum iron concentration and transferrin saturation do not quantitatively reflect body iron stores and should therefore not be used as surrogate markers of tissue iron overload".

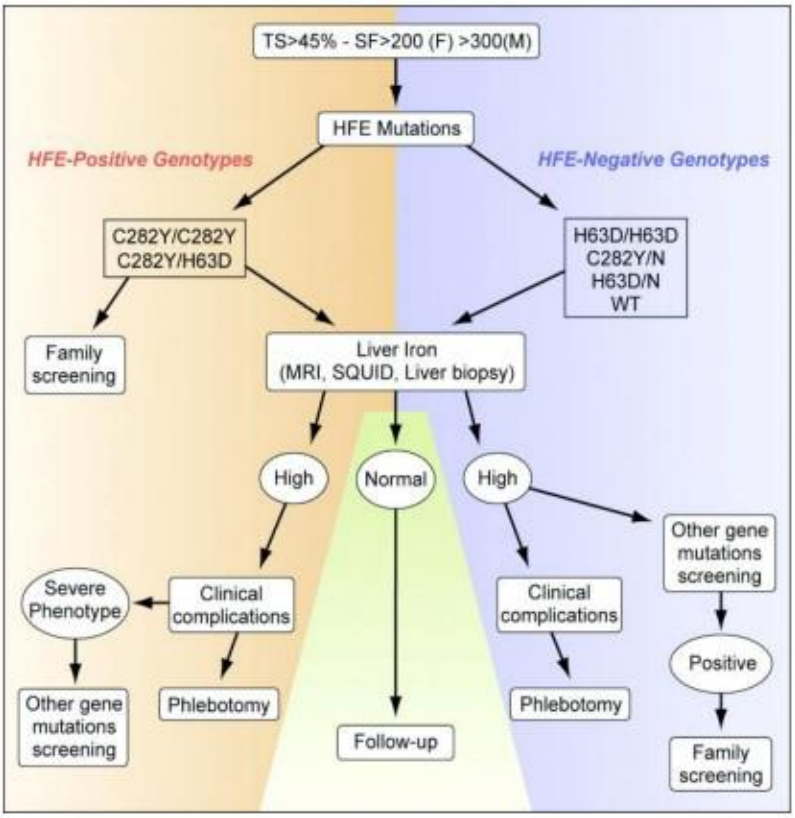

Fig 2: Flow chart for haemochromatosis diagnosis based on genotype at risk and liver iron content. Taken from Camaschella, C. Blood. 2005[3]

References:

1. *European Association for the Study of the liver. EASL Clinical Practice Guidelines for HFE Hemochromatosis.* Journal of Hepatology, 2010. doi: 10.1013/j.jhep.2010.03.001. (C) 2010 European Association for the Study of the Liver.
2. Swinkels, D.W., et al, Neth J Med, 2007. 65. 452-5.
3. Camaschella, C. Blood, 2005. 106. 3710-7.
4. Gan E.K, et al,. Seminars in Liver Disease, 2011. 31.293-301
5. Swinkels, D.W., et al, Clin Chem, 2006. 52. 950-68.

For a full list of up to date guidelines please visit www.resonancehealth.com

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