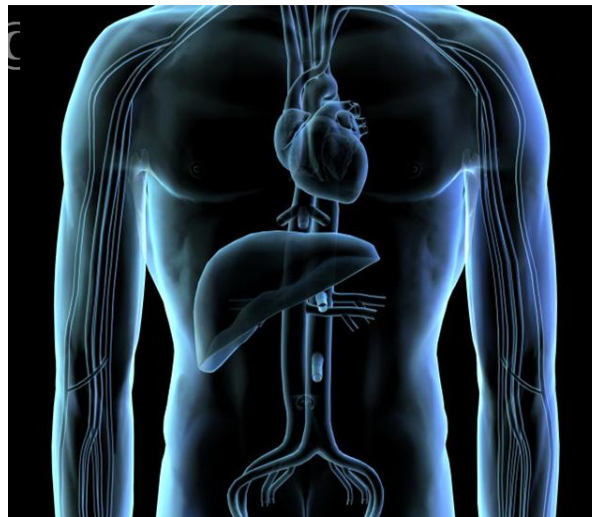


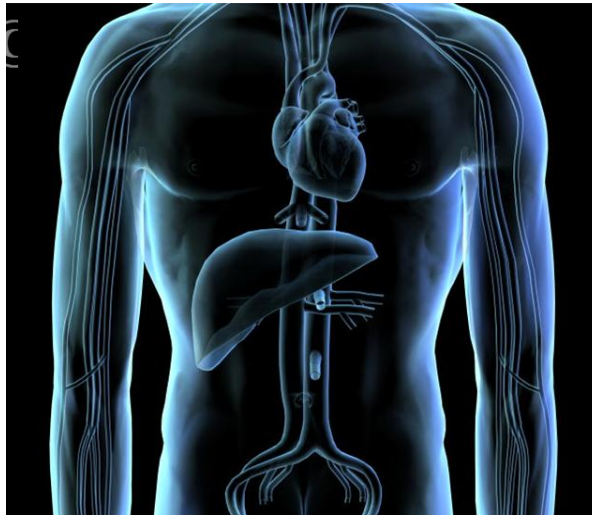
Evaluation of Iron Overload

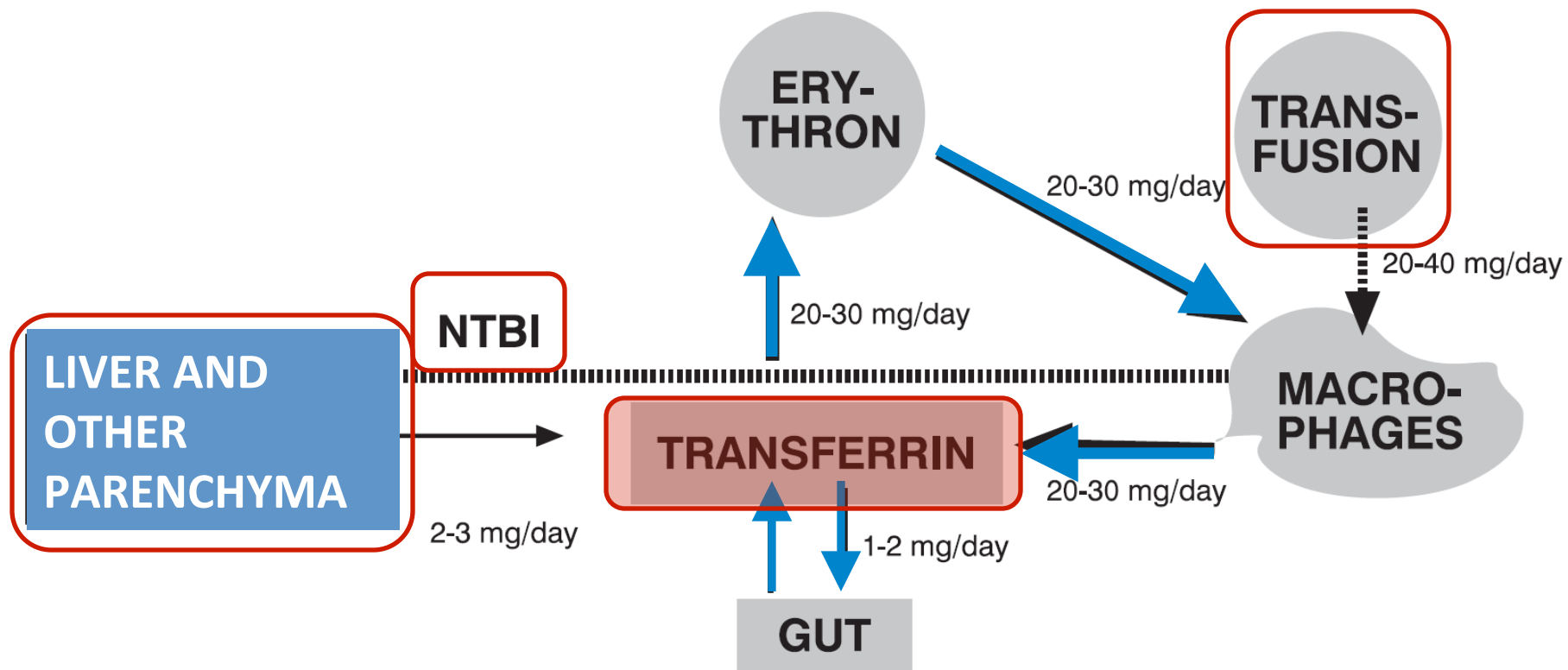


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Serum Ferritin

- < 3000 ug/L Ferritin secreted in iron-free form from macrophages
- > 3000ug/L Increasing proportion of iron-laden ferritin 'leaks' from hepatocytes

- Advantages for monitoring iron overload
 - Simple and widely available
 - Generally correlates with body iron stores
 - Associated with overall prognosis and cardiac disease in thalassemia major

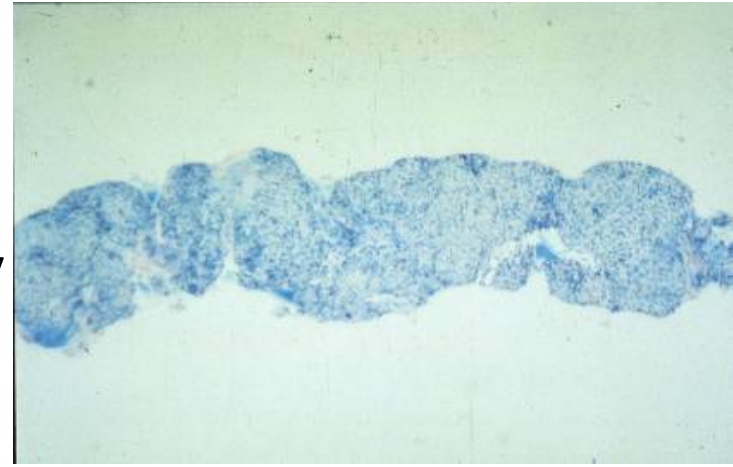
- Can be unreliable
 - Day-to-day variations
 - False increases - inflammation, hepatitis and/or liver damage
 - False decreases - vitamin C deficiency
 - Underestimate of IOL in thalassemia intermedia

Liver Iron Concentration

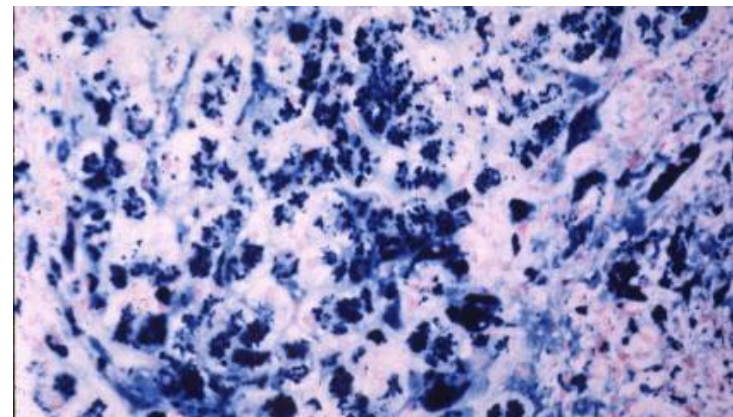
- Normal LIC = 1.8 mg/g dry wt
- < 7 mg/g dry wt seen in some non-thalassemic populations without apparent adverse effects
- LIC >15-20 mg/g associated with:
 - Worsening prognosis
 - Liver fibrosis progression
 - Liver function abnormalities

Liver Biopsy

- Advantages
 - Direct measurement of LIC
 - Validated reference standard
 - Information on liver histology/pathology
 - Correlation with morbidity and mortality



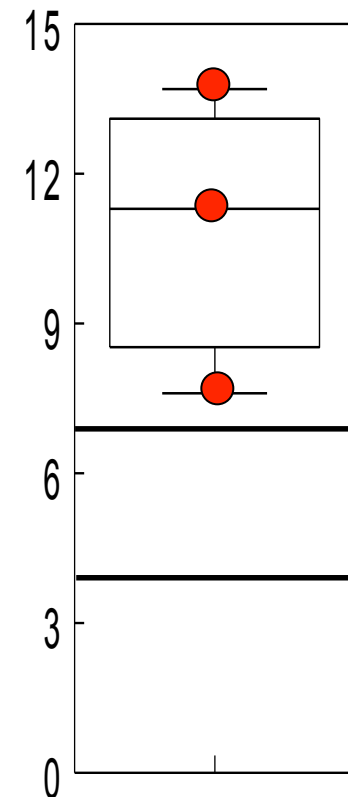
- Disadvantages:
 - Distribution artefact
 - Safety
 - Patient acceptance
 - Sample size
 - ≥ 1 mg dry weight
 - >4 mg wet weight



Porter. *Br J Haematol.* 2001;115:239.

Liver biopsy as gold standard?

- Six year old with transfusion-dependent β^+ thalassemia and Gilberts, with symptomatic cholelithiasis
- At time of cholecystectomy, three separate liver pieces of adequate weight for analysis (>1 mg dry wt)
- Mean/SD: 10.8+/- 3.3
- 7.6, 11.3, 13.7 mg/g dry wt



Noninvasive Measurement of Liver Iron

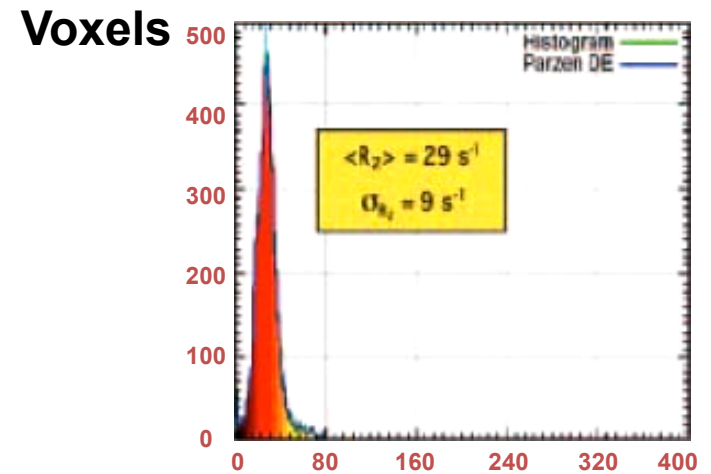
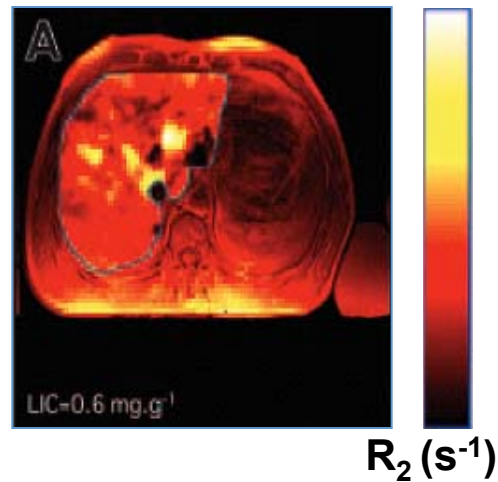
- SQUID (biosusceptometry of liver)
 - Only 4 in world. Well validated, but poor correlation with biopsy results.
- **MRI techniques**
 - Gradient echo (T2*) (single breath hold)
 - Insensitive at levels >15 mg/g¹
 - Spin echo (T2)(R₂)
 - Linear over larger range, longer acquisition time of 20-40 minutes²
 - Gradient with Signal Intensity Ratio³
 - Spin echo with Signal Intensity Ratio⁴

MRI = magnetic resonance imaging; SIR = signal intensity ratio.

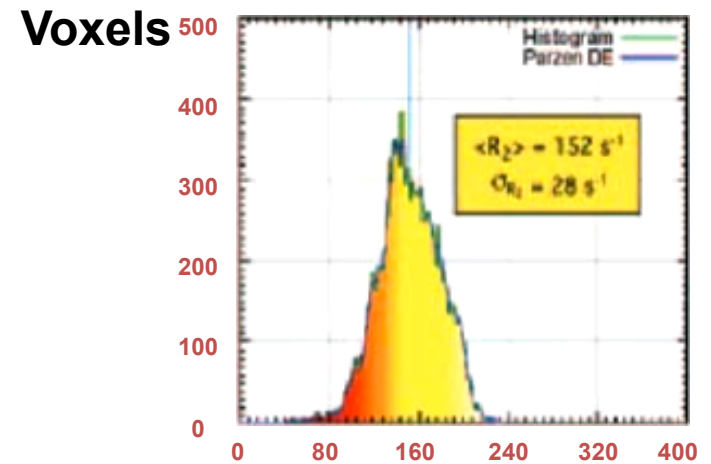
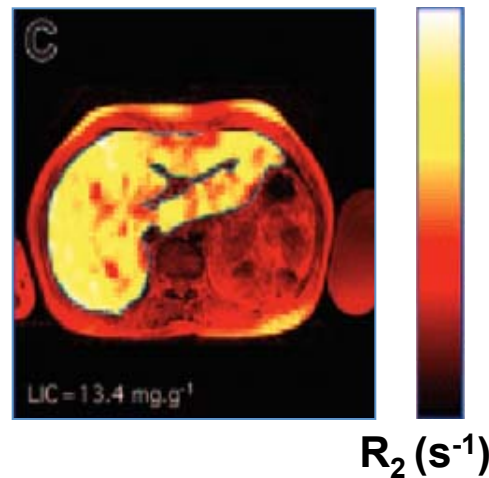
1. Anderson. *Eur Heart J*. 2001; 2. St Pierre. *Blood*. 2005; 3. Gandon. *Lancet*. 2004; 4. Jensen. *Blood*. 2003.

R₂ Transverse Relaxation Rates

Nonoverload



Thalassemia major



“Ferriscan[®]”

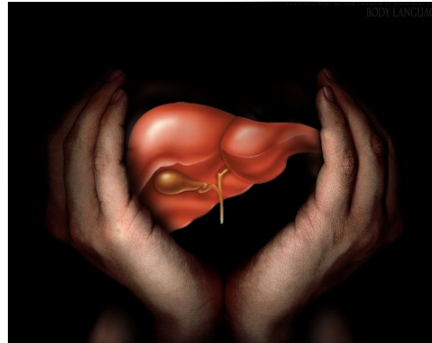
St Pierre et al. *Blood*. 2005;105:855.

Transverse relaxation rate R₂ (s⁻¹)

R2 Liver MRI – “FerriScan”

- MRI machine must be calibrated with a Phantom supplied by company
- Data sent via internet for analysis by Ferriscan software
- Payment per scan analysed
- Technique can be applied with little training, at any centre with a reasonably up-to-date MRI machine

Limitations of Liver Iron Concentration (as a sole monitoring tool)



- ***Liver iron does not parallel heart iron***
 - Patients can develop heart failure with low levels of liver iron
 - Duration of exposure may be as important as maximum value?
 - Need to look at entire history of liver iron?
 - Hypothesis: If certain threshold never exceeded, unlikely that heart will accumulate iron

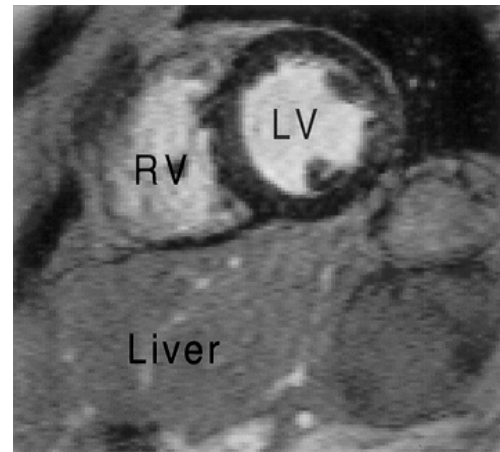
Thalassemia and Cardiac Iron by T2* proton MRI Liver & heart in same slice



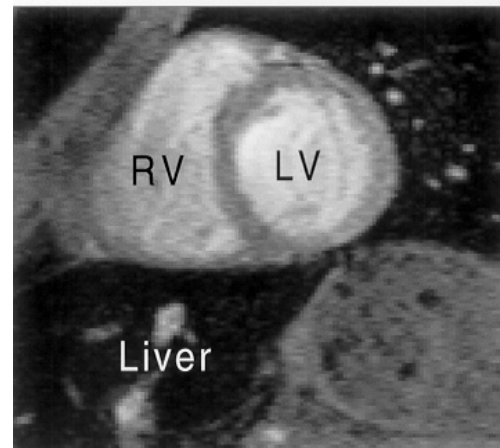
Children's Hospital, Boston; Andy Powell, MD

Discordance of Liver and Heart Iron

**Severe cardiac iron
Minimal liver iron**



**Severe liver iron
Minimal cardiac iron**



Cardiac Iron – T2* MRI

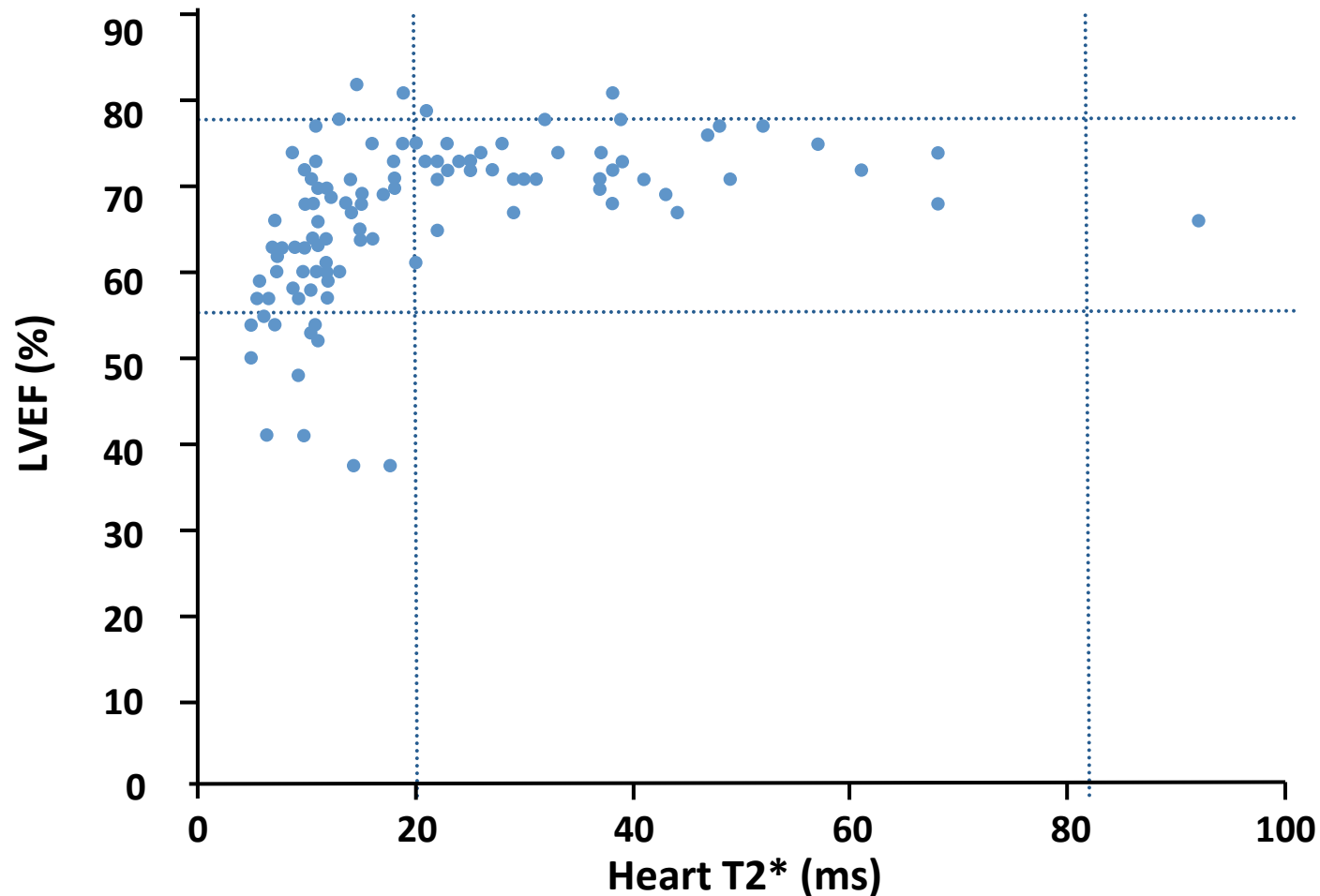
- Measures proton relaxation time in msec
- Shortened in presence of iron
- T2* predicts risk of impaired left ventricular function

T2* Value	Risk of impaired LV function
>20 msec	Normal
10-20 msec	Up to 10%
8-10 msec	18%
6 msec	38%
4 msec	70%

- Disadvantages:
 - Requires expertise and standardization
 - Complex risk factors for developing heart failure
 - T2* measures storage iron – not in itself directly toxic to cells
 - Other factors may increase labile intracellular iron (e.g. myocarditis, or lack of continuous chelation)

Anderson et al, 2001; Westwood, 2007

Heart T2* <20 ms Associated With Low LVEF; <8 ms highest risk

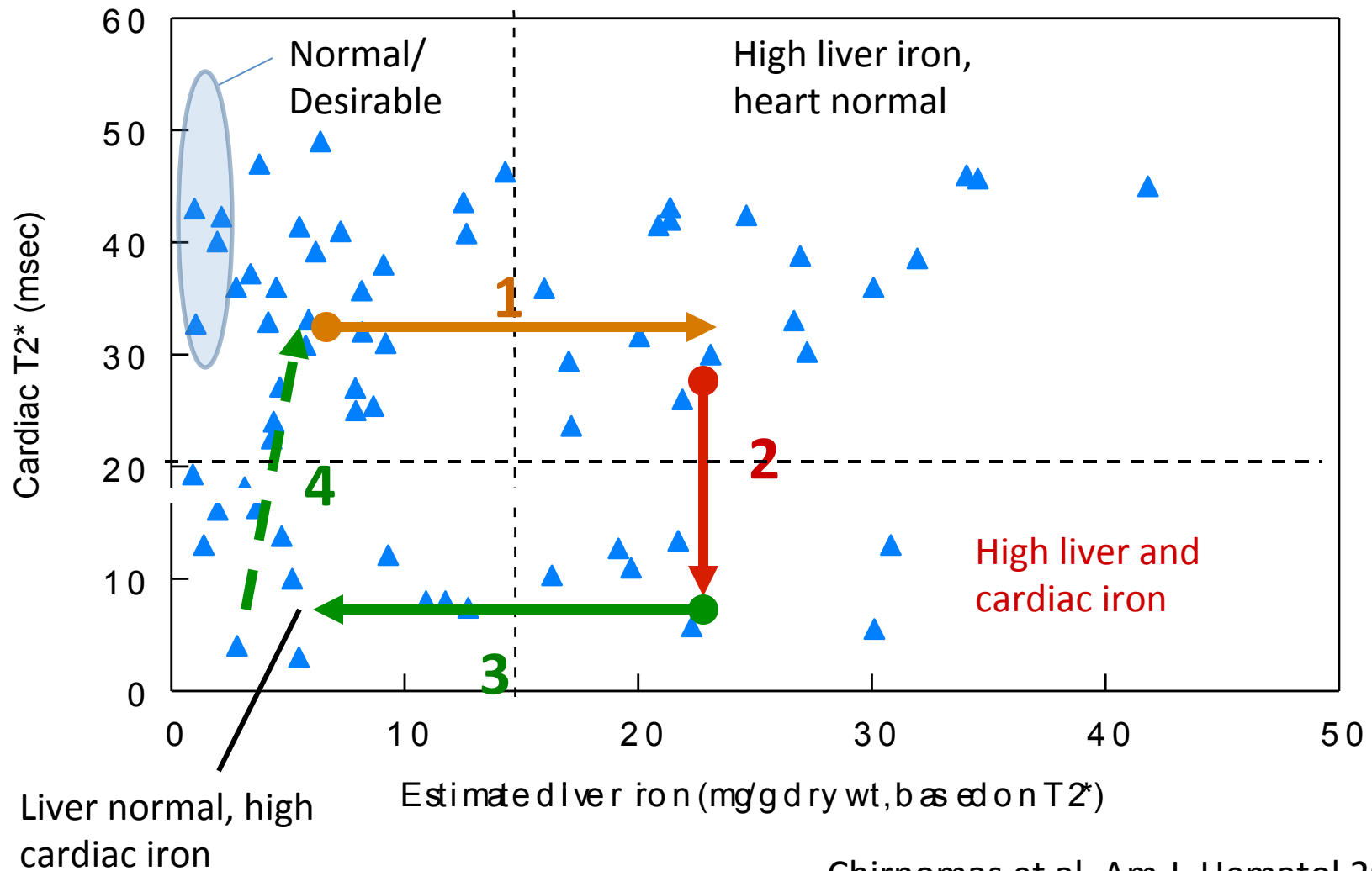


LVEF = left ventricular ejection fraction.

Anderson et al. *Eur Heart J.* 2001;22:2171.

MRI Heart and liver iron assessment - "snapshot" view

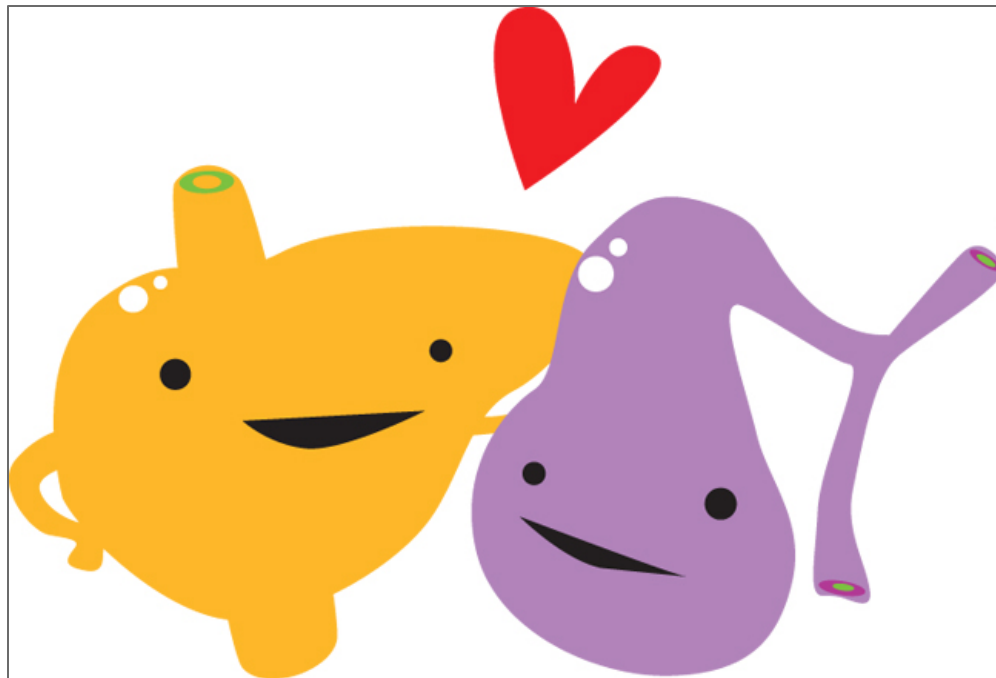
Boston Children's data 2004-2007



Other methods of measuring iron overload

- Urinary iron excretion
- NTBI or labile plasma iron assay

Thank you
Questions?



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