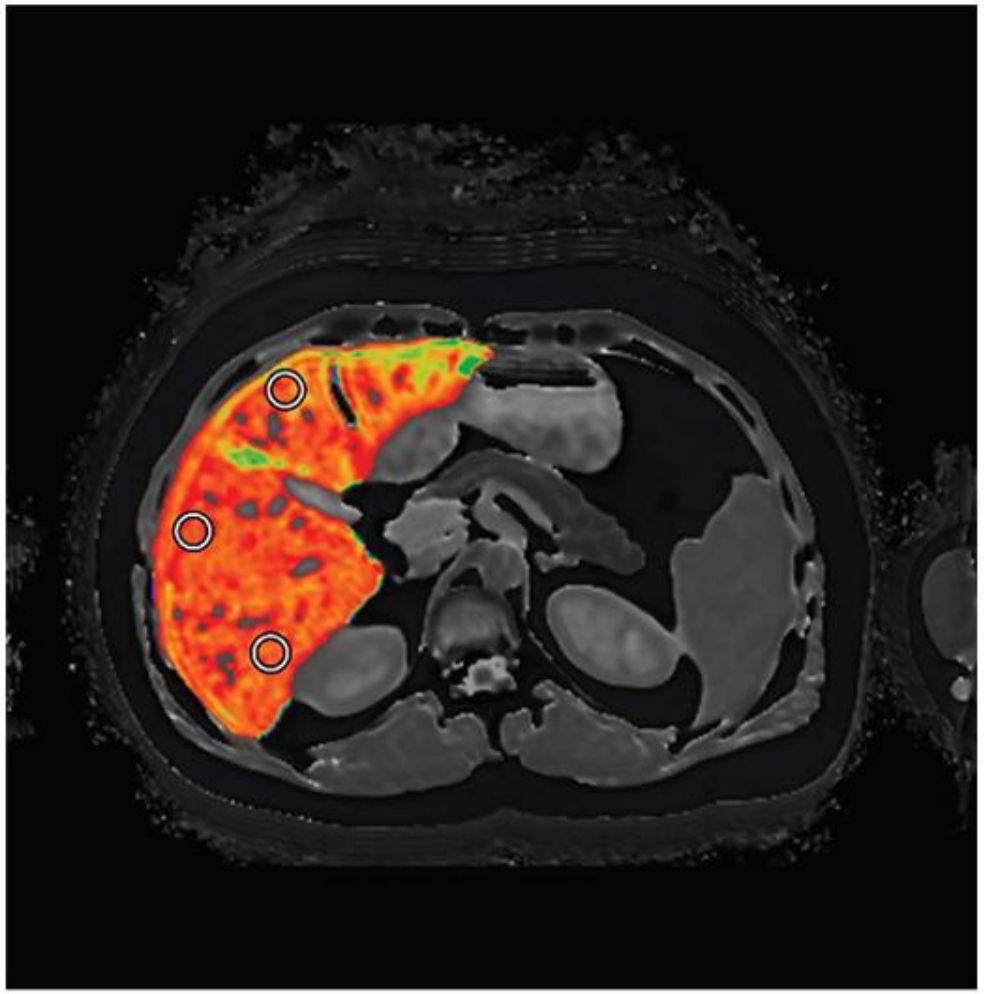
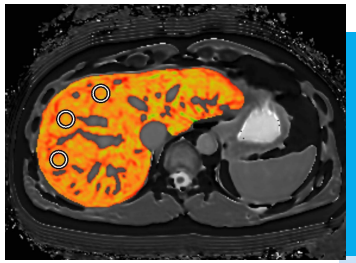
Multiparametric MRI in Autoimmune liver disease

Perspectum

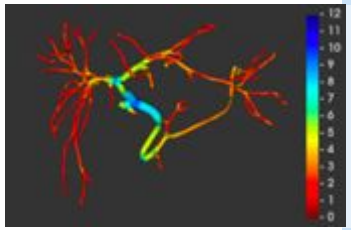


Perspectum's Product Suite



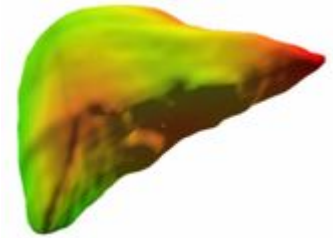
LiverMultiScan®

Quantitative, non-invasive MR analysis software for patients with chronic liver disease



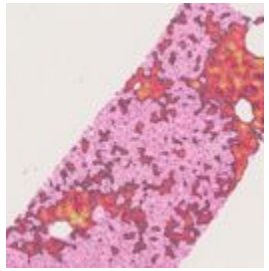
MRCP+™

Quantitative biliary imaging tool, using computational techniques to enhance and visualise biliary structures



HepaT1ca™

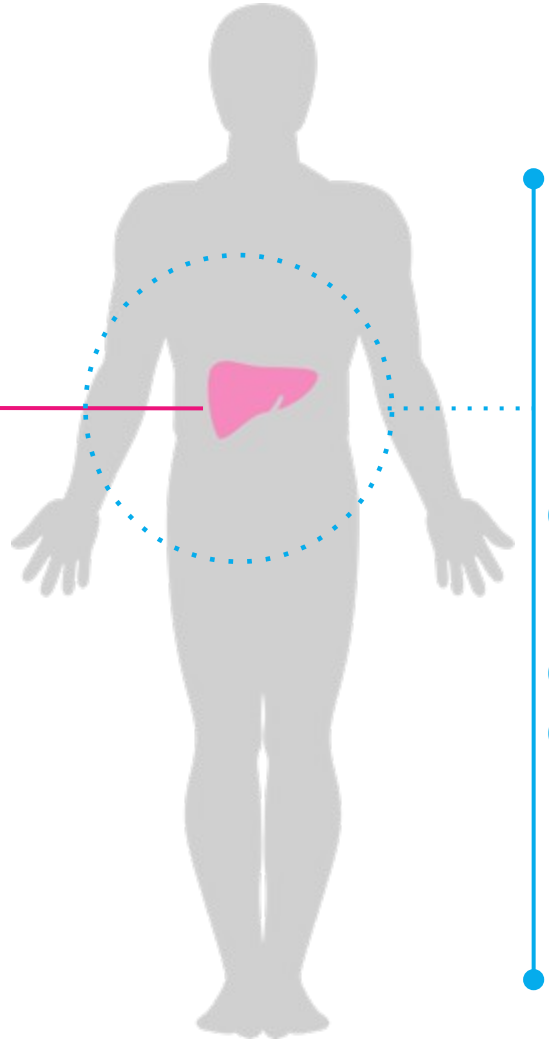
Liver health measurement technique for the evaluation of surgical risk in cases of hepatic resection



Digital Pathology

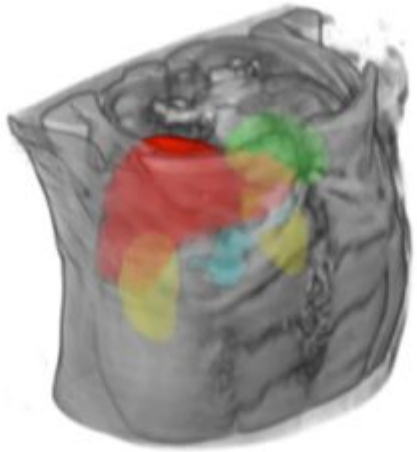
Vial to file service for standardized and more accurate reads in NASH trials

Hepatobiliary Imaging



Multi-organ Imaging

Multiorgan health measurement technique to quantitatively assess the heart, kidneys, liver, pancreas and spleen

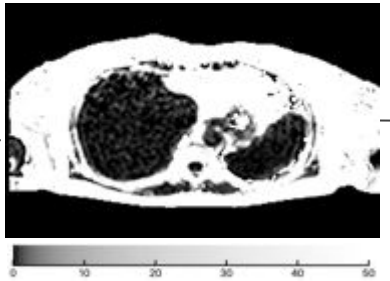


Liver*MultiScan*: FDA-cleared precision imaging for every patient

Quantitative MRI imaging biomarker correlates with histology

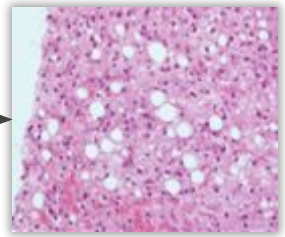
In a single contrast-free MRI scan

MRI-PDFF (%)

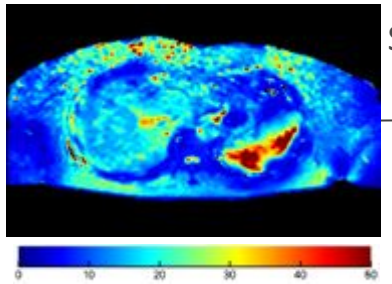


Shown to correspond to histological measures of ***steatosis***

Steatosis[1]

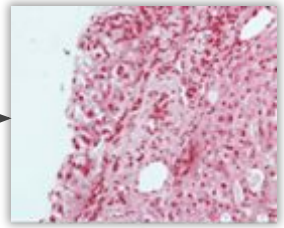


T2* (ms)

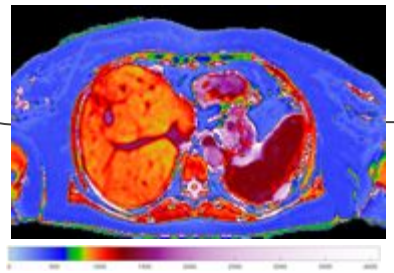


Shown to decrease with increased ***hepatic iron overload***

Iron concentration[2]

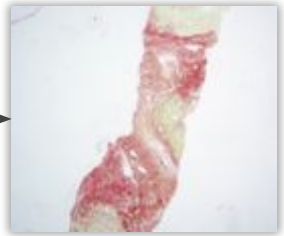


cT1 (ms)



Free-water content in tissue shown to increase in ***inflammation and fibrosis***

Fibro-inflammation[3]



510(k) CE

#includes patient preparation time

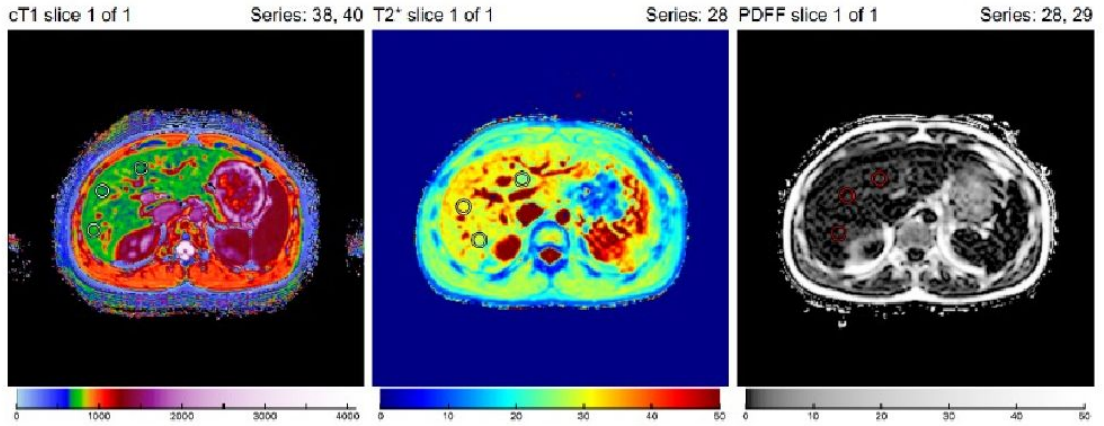
1. Idilman et al., 2013; Reeder et al., 2017.
2. Wood et al., 2005; Hoad et al., 2015.
3. Banerjee et al., 2014; Pavlides et al., 2017.

Comprehensive Liver Tissue Characterization

Single scan, highly reproducible, quantifying components of liver disease

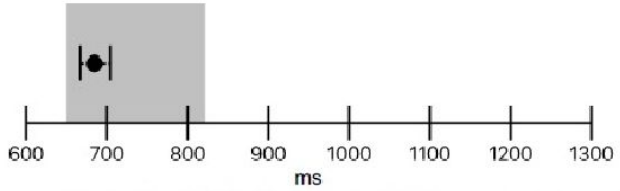
Healthy Patient

cT1 (ms)	T2* (ms)	PDFF (%)
Median: **685ms**	Median: **28.2ms**	Median: **0.8%**
IQR: 667 to 704ms	IQR: 26.1 to 31.1ms	IQR: 0.4 to 1.2%
Ref interval:633 to 794ms[A]	Normal:>20.0ms at 1.5T[B]	Normal:<5.6%[C]
cT1 is corrected for iron and field strength	T2* is dependent on field strength	



cT1 (corrected T1)

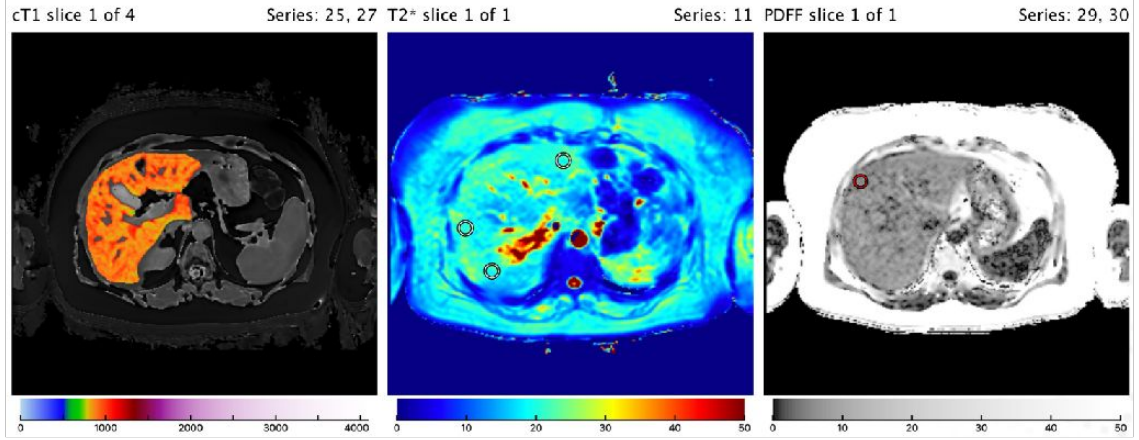
Median: 685ms
IQR: 667 to 704ms
Ref interval: 633 to 794ms[A]
1 slice, 3 regions of interest



Metrics are displayed as median with interquartile range (filled circle and tails). They are calculated from one or more regions of interest (circles overlaid on the images), in some cases over more than one slice. Calculated metrics are shown against a reference normal range at 3T (grey box). The clinician must be cautious when interpreting cT1 and, in particular, be aware of the non-meaning of colour.

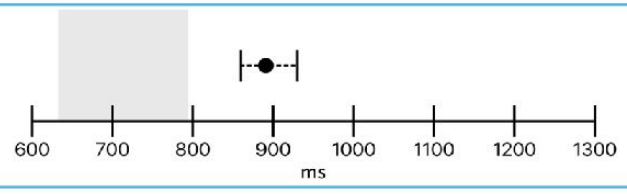
AIH Patient

Whole liver cT1 (ms)	Liver ROI T2* (ms)	Liver ROI PDFF (%)
Median: 891ms	Median: 20.7ms	Median: 6.0%
IQR: 860 to 930ms	IQR: 19.6 to 21.7ms	IQR: 5.0 to 7.0%
Ref range: 633 to 794ms	Reference: >12.5ms at 3T[A]	Reference: <5.6%[C]
cT1 is corrected for iron and field strength[A]	T2* is dependent on field strength	PDFF generated with the IDEAL method



cT1 (corrected T1)

Median: 891ms
IQR: 860 to 930ms
Ref range: 633 to 794ms
4 slices



Metrics are displayed as median with interquartile range (filled circle and tails). They are calculated from whole liver regions of interest or one or more slices (overlaid in color on the image). Calculated metrics are shown against a reference range at 3T (gray box). The clinician must be cautious when interpreting cT1 and, in particular, be aware of the non-meaning of color.

Autoimmune Hepatitis

Autoimmune hepatitis

A treatable liver disorder with many unmet needs

Non-resolving condition, treated with a combination of corticosteroid and immunosuppressant therapy.

Rare disease with prevalence of 15-25 **cases per 100,000** in Europe (approx. **10,000** individuals within the UK); **11%-23%** of patients with chronic liver disease in the US and accounts for **4-6%** of adult liver transplant cases

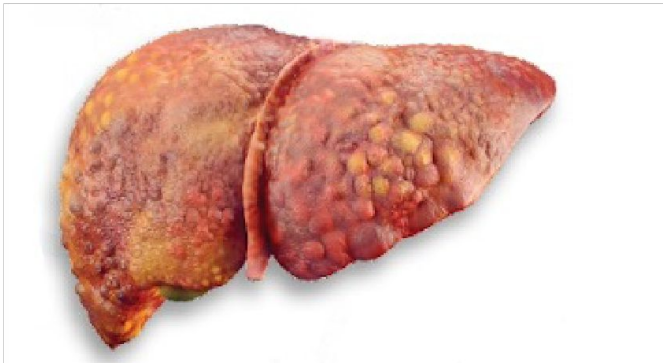
Management requires **regular blood tests** and balance between corticosteroids and immunosuppressants to balance disease control and unwanted side effects of treatment

Blood test lack sensitivity and lag-behind hepatic events.

Biopsy is invasive and does not capture disease heterogeneity.

Healthy Liver

AIH Liver



Addressing unmet needs in AIH using LiverMultiScan

Improving diagnosis, monitoring and risk stratification

Diagnosis

- A non-invasive **adjunct to liver biopsy** for staging disease

Treatment Response

- **Replaces serial liver biopsy.** A superior test for **non-invasive monitoring** of treatment response that can positively **impact physician management plans**

Prognosis

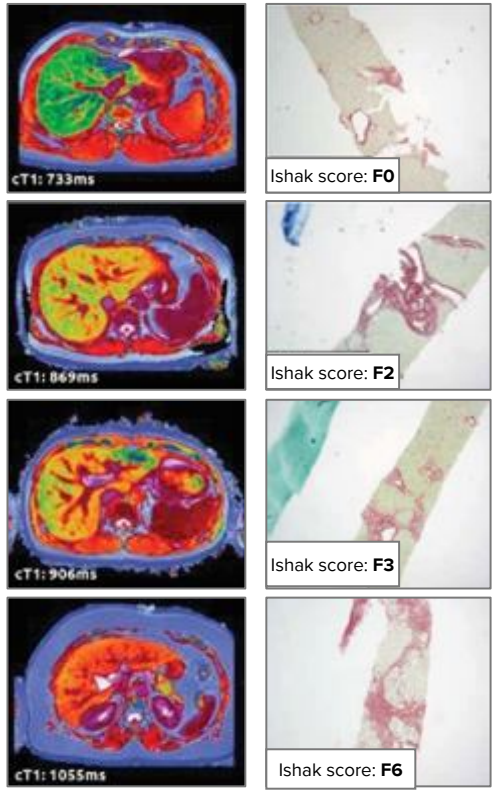
- A personalised medicine approach to management of disease, with biomarkers of prognostic value that can **minimise the risk and costs associated with flares** and guide appropriate decision on second line therapies

Utility of LiverMultiScan (cT1)

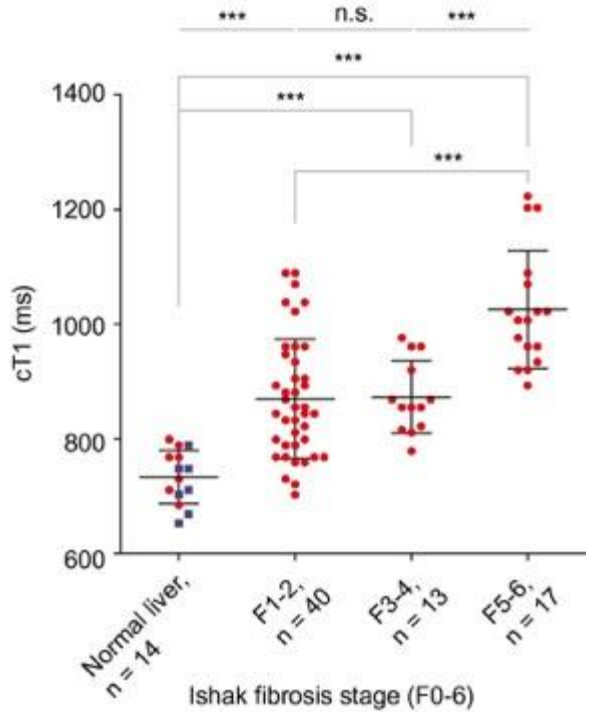
- Aid diagnosing AIH
- Precise patient monitoring
- Predict clinical outcomes
- Characterise disease heterogeneity
- Aid drug development

cT1 to stage chronic liver disease

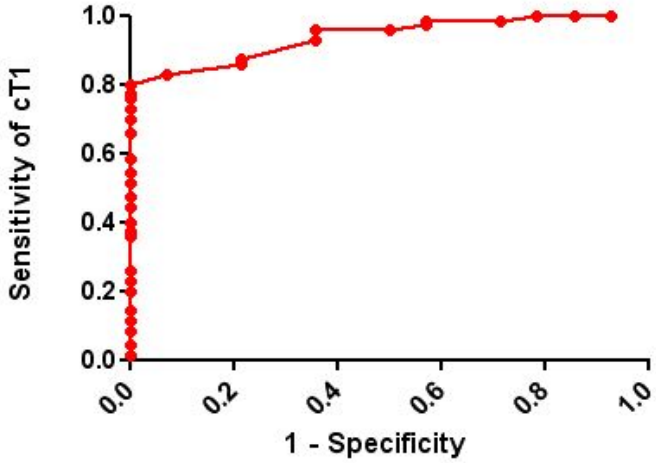
Non-invasive test to identify early fibrosis in CLD patients from varying aetiologies



cT1 values vs biopsy-proven fibrosis stage in 77 CLD patients*



ROC curve of cT1 for diagnosing presence of any fibrosis (Healthy+F0 vs F ≥1)



AUROC is **0.94** (95% CI 0.89 – 0.99)
sensitivity 86%, specificity 93%

cT1 correlates with biopsy data (Ishak fibrosis score)
with excellent accuracy for diagnosing presence of any fibrosis (F ≥1).

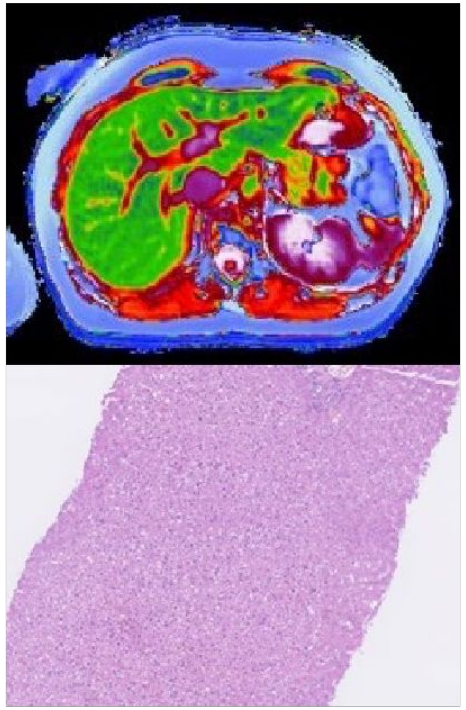
*Graph includes 7 healthy volunteers (in grey) assumed to have normal liver
ROC, Receiver Operating Characteristic; **AUROC**, Area Under ROC

JOURNAL OF HEPATOLOGY
Banerjee et al. J Hepatol., 2014.

cT1 to stage chronic liver disease

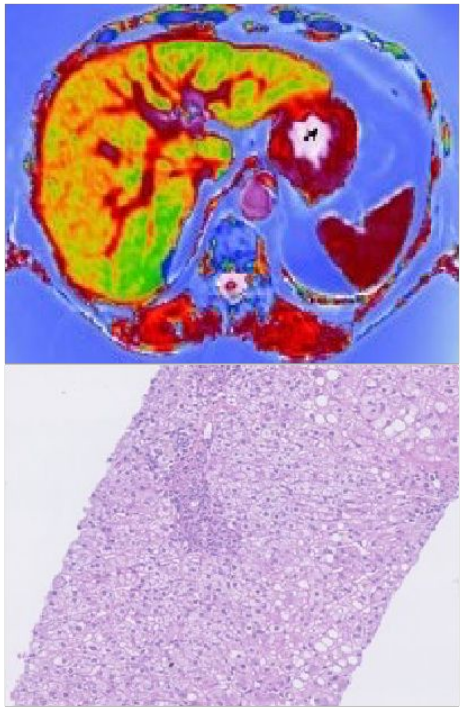
Non-invasive test to identify early inflammation and ballooning in AIH patients

Normal



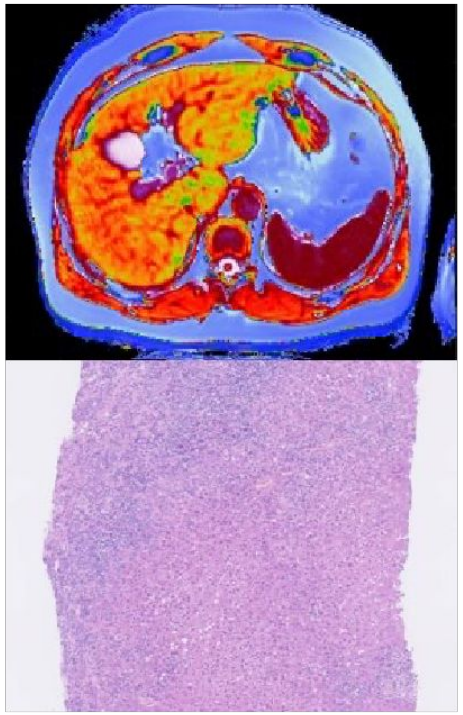
Evenly spaced nuclei, no inflamed regions

AIH – moderate cT1

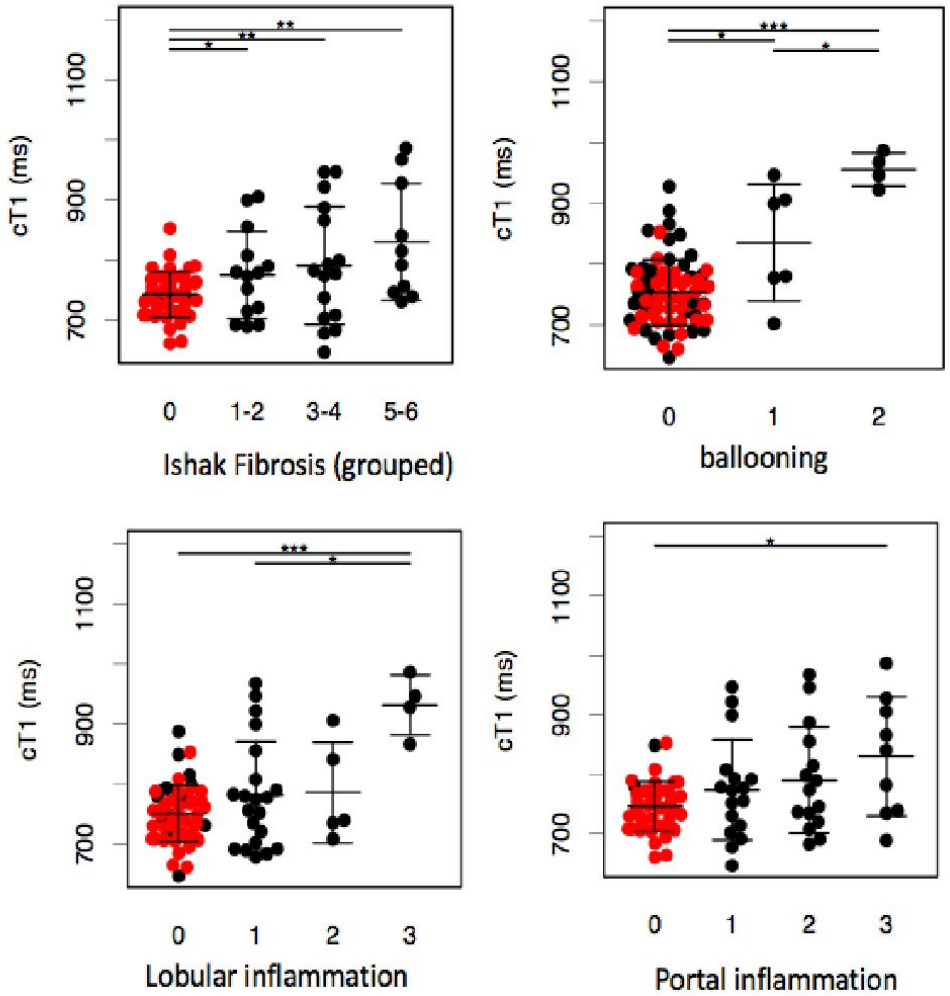


Darker more densely packed nuclei show inflamed regions

AIH – High cT1



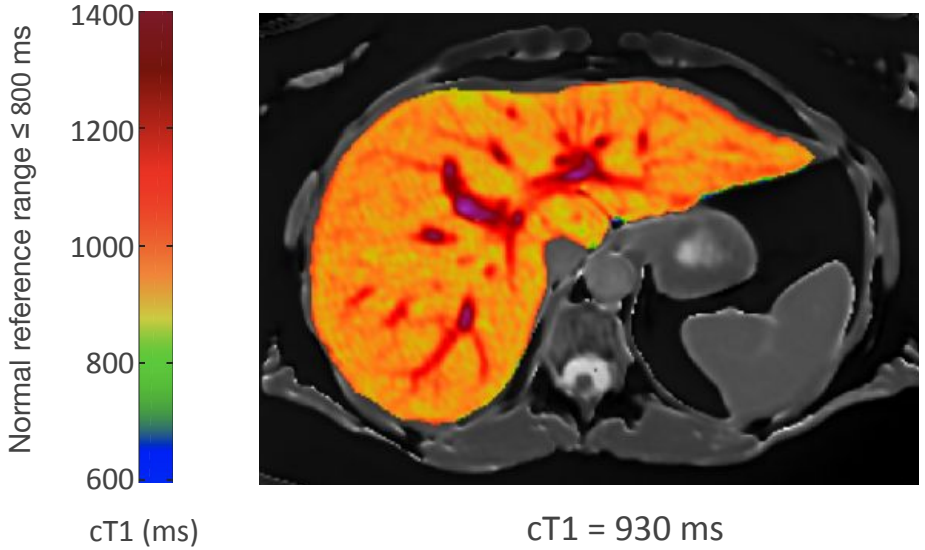
Darker more densely packed nuclei show inflamed regions.



Janowski, K et al. AASLD, 2017

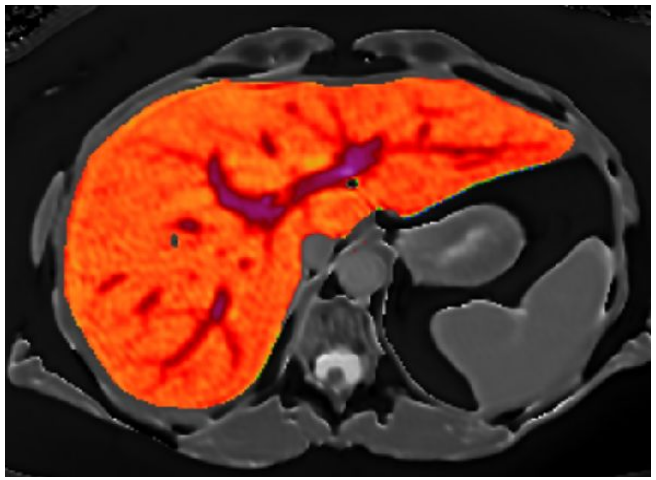
Liver*MultiScan*® cT1® is the best non-invasive predictor of disease activity in AIH

Baseline scan: Elevated cT1 shows active sub-clinical disease despite biochemical remission



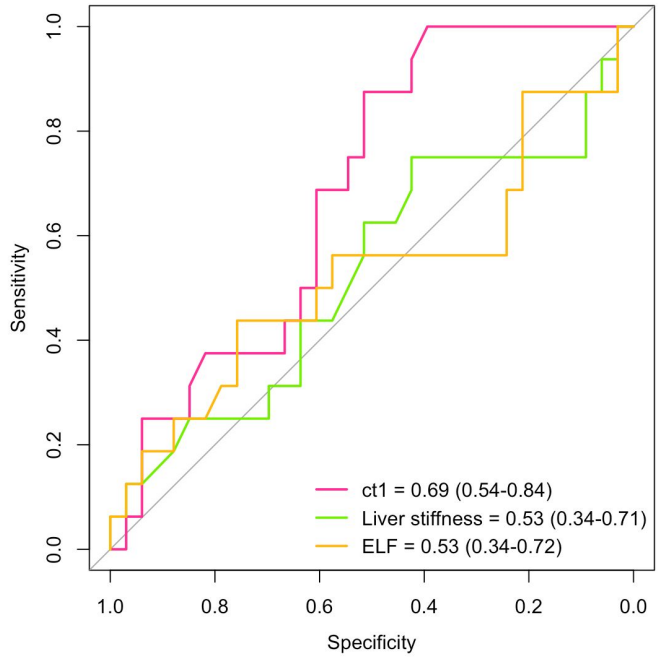
cT1 = 930 ms
ELF = 9.84
VCTE = 6.1 kPa

Follow-up scan ≤ 12 months: Elevated baseline cT1 levels predictive of relapse within 12 months



cT1 = 1092 ms
ELF = 0.01
VCTE = 7.6 kPa

Performance of surrogate biomarkers for prediction of disease activity (n=62)



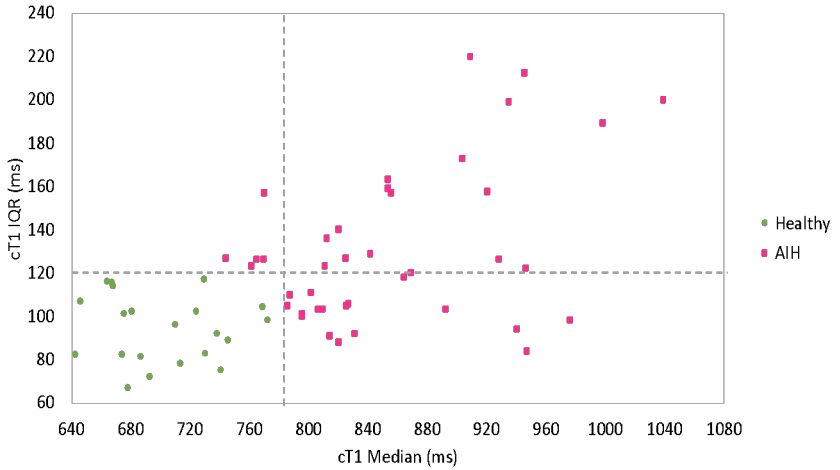
Liver*MultiScan*'s cT1 outperformed FibroScan® TE (transient elastography) and ELF blood test, emphasising its potential to influence clinical treatment and so reduce likelihood of disease progression.

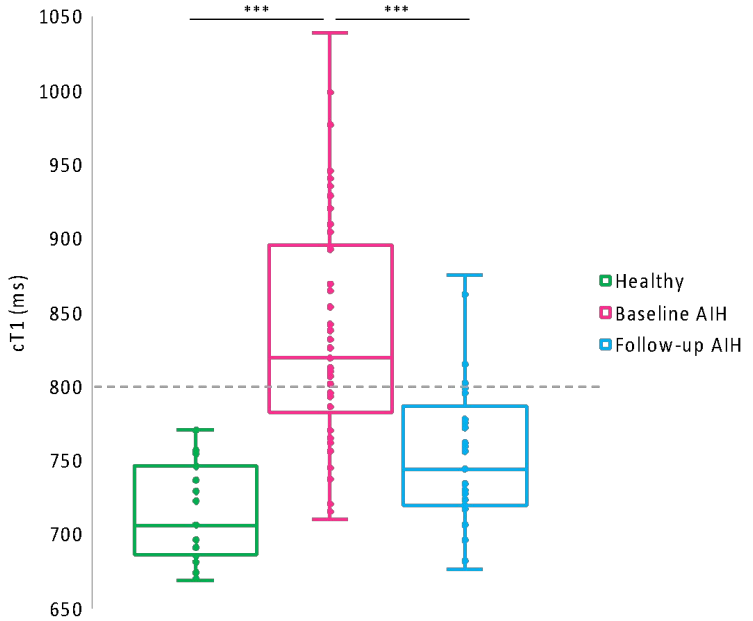
cT1 – corrected T1, LiverMultiScan's measure of fibro-inflammation; IQR – Interquartile range;
Liver stiffness – using FibroScan; ELF – Enhanced Liver Fibrosis blood test

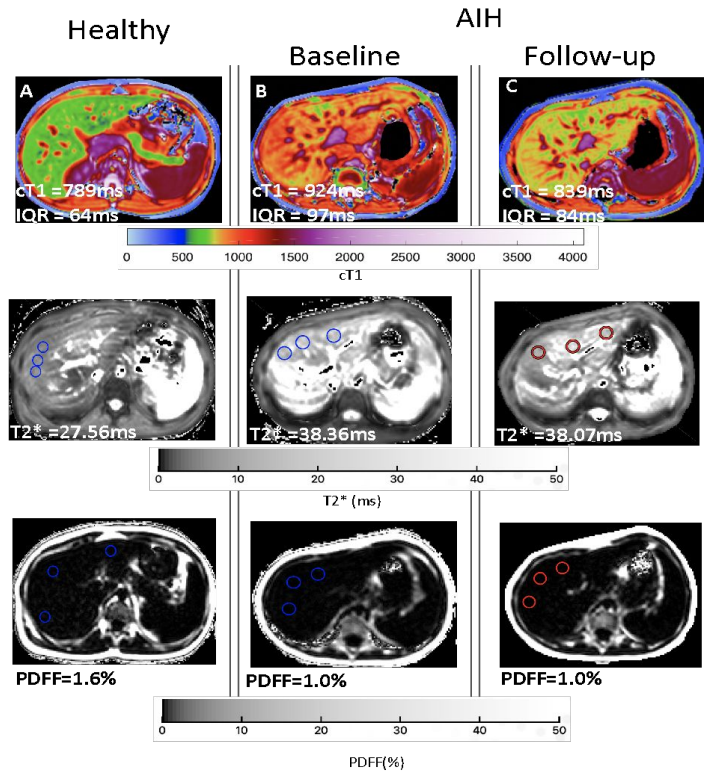
HEPATOLOGY COMMUNICATIONS

Arndtz et al. (2021) Hepatology Communications, 5(6):1009-1020

cT1 as a Non-invasive Monitoring Tool for Paediatrics with AIH







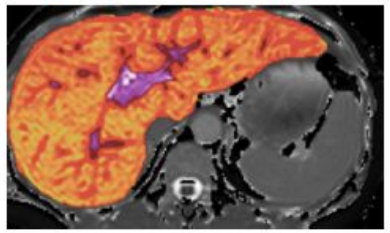
cT1 can stratify between healthy and AIH patients as well as identify those with active sub-clinical disease (histologically confirmed) despite biochemical remission (normalised AST, ALT and IgG).

Janowski, K et al. JPGN, 2020

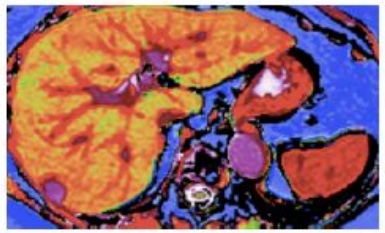
cT1 as non-invasive tool for monitoring disease progression from diagnosis in AIH

All patients in biochemical remission

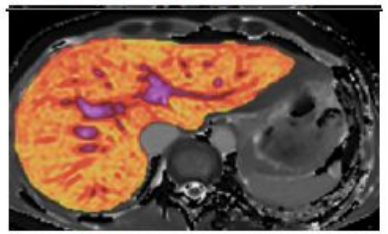
Patient 1: cT1 927ms,
F4, ALT 34 U/L, IgG 14 g/L



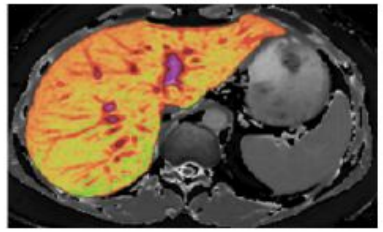
Patient 2: cT1 880ms,
F1, ALT 30 U/L, IgG 14 g/L



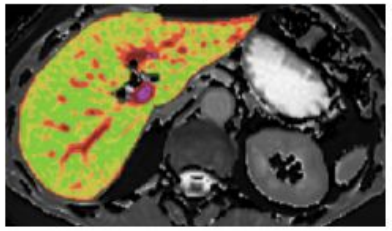
Patient 3: cT1870ms
F1, ALT 28 U/L, IgG 13.2 g/L



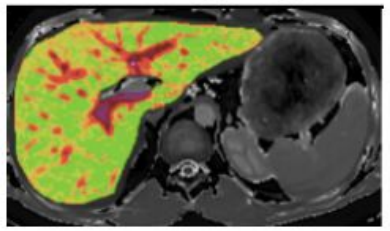
Patient 4: cT1 840ms
F1, ALT 26 U/L, IgG 9.8 g/L



Patient 5: cT1 798ms
F1, ALT 37 U/L, IgG 13.2 g/L

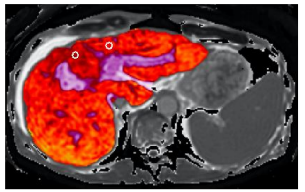


Patient 6: cT1 772ms
F1 , ALT 35 U/L, IgG 9.2 g/L

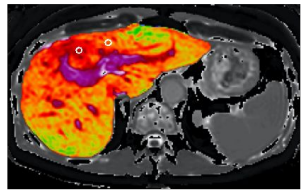


Change in cT1 over 6 months

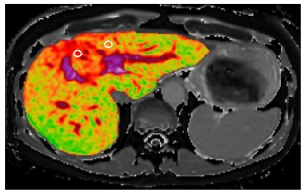
Baseline



Month 1



Month 6



cT1 (ms)	1069	910	831
cT1 IQR (ms)	181	226	175
% of liver with cT1>800ms	99%	83%	64%

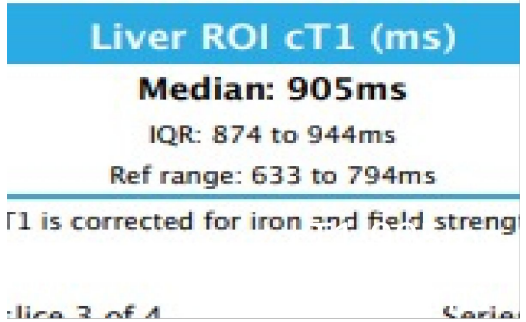
cT1 correlates strongly with both blood markers and histology (mHAI) at diagnosis, and a better monitor of disease than blood markers in the first 6months of treatment.

Hartl et al 2021 EASL2021

cT1 IQR a measure of disease heterogeneity

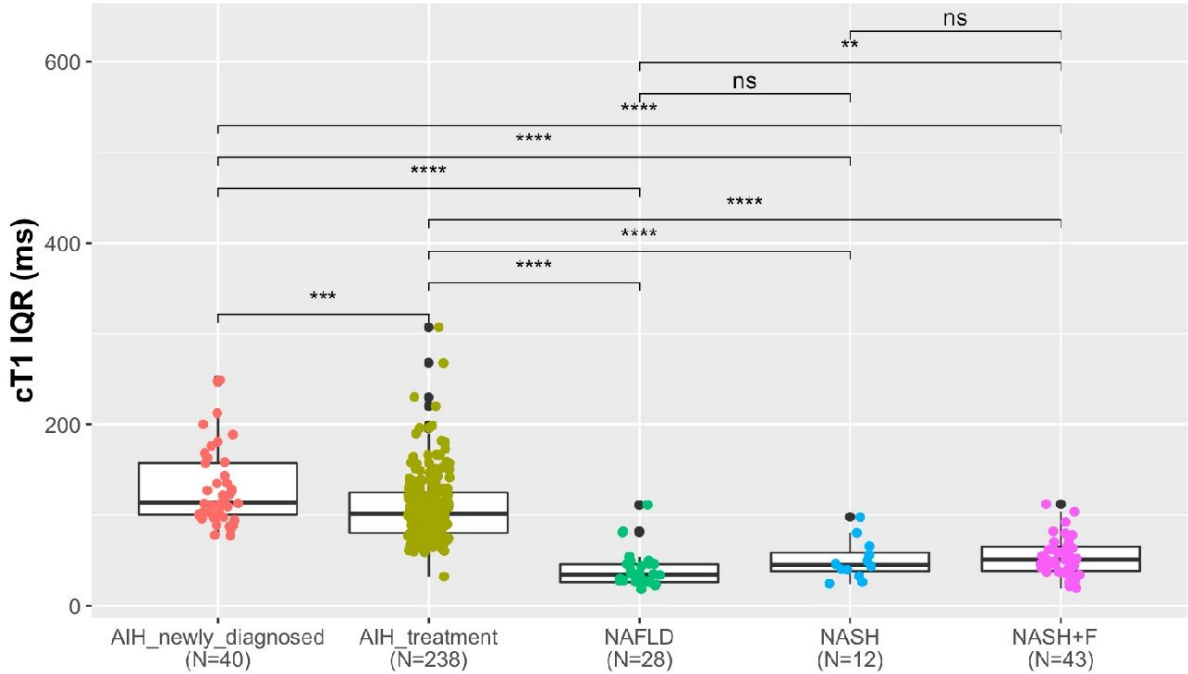
cT1 interquartile range (IQR) distinguishes between heterogeneous and homogeneous liver diseases

NASH + Fibrosis



AIH

Boxplots of heterogeneity in fibro-inflammation (cT1 IQR)

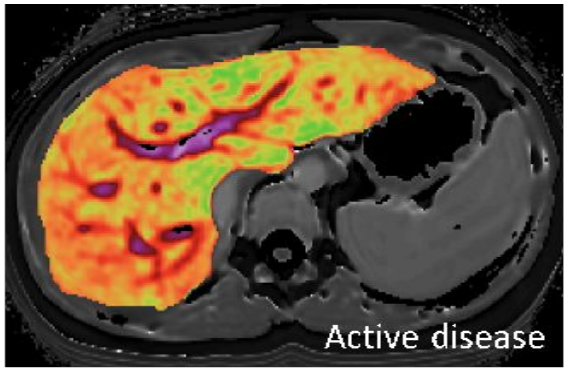


cT1 IQR has excellent diagnostic accuracy (AUC:0.98) to distinguish AIH from NAFLD/NASH and may reflect heterogeneity differences in liver fibroinflammation and therefore pathophysiology

Shumbayawonda E, et al. AASLD 2021

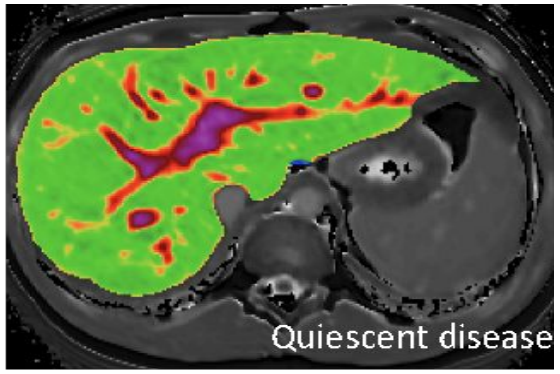
cT1® identifies patients with quiescent disease who may benefit from a change in treatment

Diagnosis

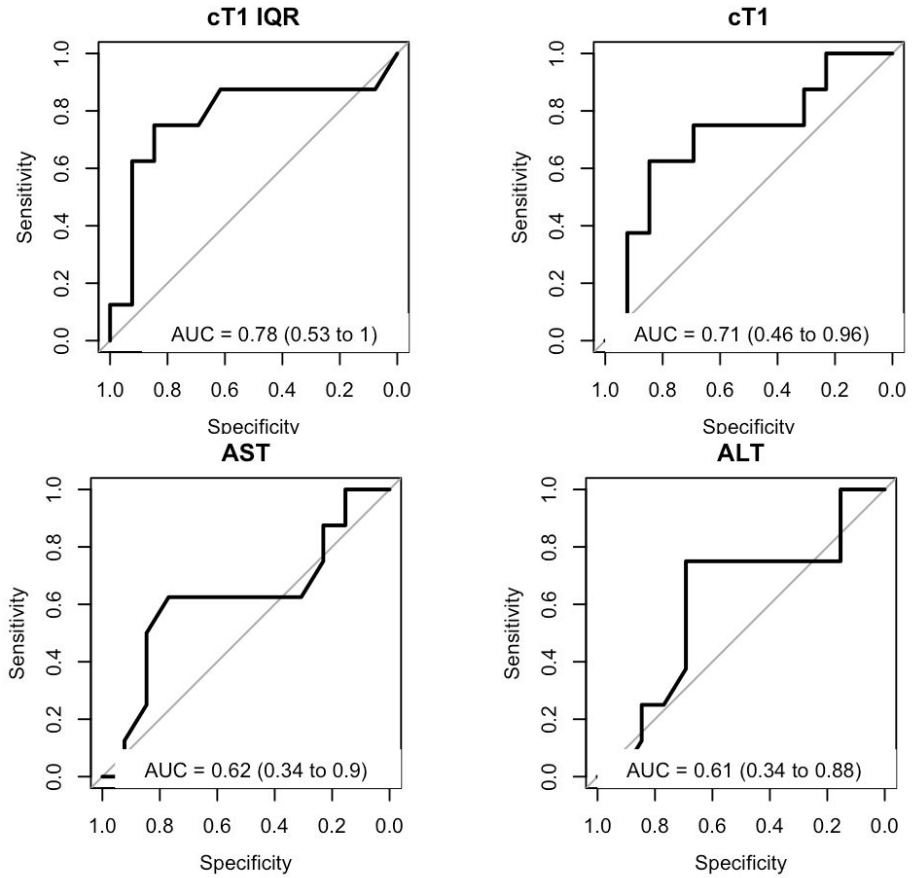


AST: 55 IU/L
ALT: 87 IU/L
Fibrosis: 5
Portal inflammation: 3
Lobular inflammation: 2
cT1: 917 ms

Follow-up



AST: 21 IU/L
ALT: 20 IU/L
Fibrosis: 0
Portal inflammation: 0
Lobular inflammation: 1
cT1: 749 ms



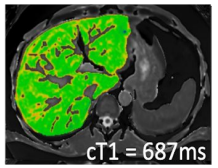
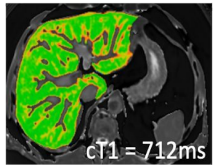
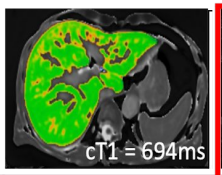
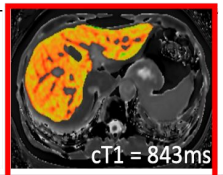
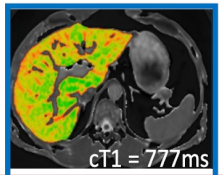
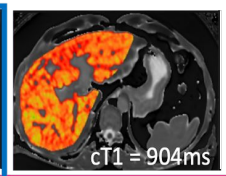
Diagnostic accuracy of imaging and blood biomarkers to identify AIH patients with quiescent disease.

cT1 and cT1 IQR have utility in identifying paediatric patients with quiescent disease having no underlying active disease who may benefit more from a change in treatment, thus offering a potential non-invasive alternative to repeat biopsy.

Shumbayawonda E, et al. AASLD 2021

Liver*MultiScan*® detected earlier stages of treatable disease in patients with autoimmune hepatitis to allow tailored treatment[1]

- First-of-its-kind study to look at physician-reported confidence in **Liver*MultiScan*** for clinical management of AIH.
- Physician's confidence increased significantly (from 7 to 9/10) after viewing Liver*MultiScan* reports.
- **cT1** better characterized disease activity, compared to serum biomarkers and liver stiffness measures.

	Deep biochemical remission		Normal biochemical remission		Biochemically active disease	
						
cT1 (ms)	687	712	694	843	777	904
pcT1 (%)	7	11	9	46	34	94
AST (IU/L)	19	19	25	38	144	159
ALT (IU/L)	16	18	25	38	299	196
IgG (IU/L)	10.5	11.4	11.1	11.7	14.5	26.8
Liver stiffness (kPa) using VCTE	6.6	3.2	6.6	4.1	6.6	31.2

cT1, pcT1, serum biomarker and liver stiffness measures for patients with AIH classified into remission stages according to their liver enzyme results. When patients were classified using cT1 (cT1 >800ms is indicative of active sub-clinical disease), 7/34 of patients in normal biochemical remission had cT1 >800ms, indicating active sub-clinical disease and risk of disease relapse and 9/25 patients with "mild" active disease had cT1 <800ms.

Liver*MultiScan*'s cT1 improved AIH management by identifying patients in biochemical remission with undetected, active sub-clinical disease at a high risk of disease flare.[1]

AIH - autoimmune hepatitis; cT1 - iron-corrected T1; pcT1 - percentage of liver with active fibro-inflammation (having cT1 >800ms)
AST - aspartate transaminase; ALT - alanine transaminase; IgG - immunoglobulin G; VCTE - vibration controlled transient elastography

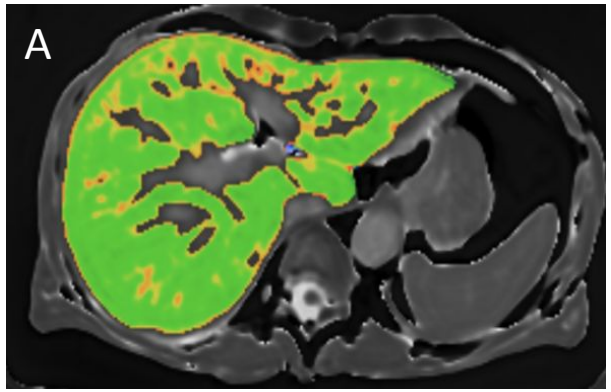
1. Heneghan et al. (2022) EClinicalMedicine

LiverMultiScan as an aid in drug development

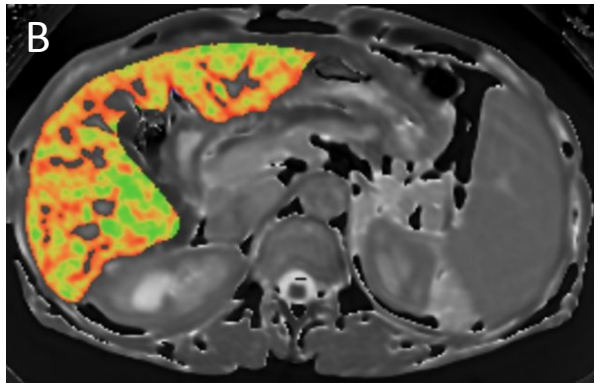
cT1 as a biomarker in AIH – Staging

Identifying patients with active sub-clinical disease despite being in biochemical remission.

cT1 is an inclusion criterion for active disease population



BMI	22.7
ALP	74
GGT	16
ALT	25
AST	25
albumin	47
bilirubin	10
Total serum globulins	27
igg	11.1
platelets	303
Treatment	Budesonide
PDFF	2
cT1	694
Age	56



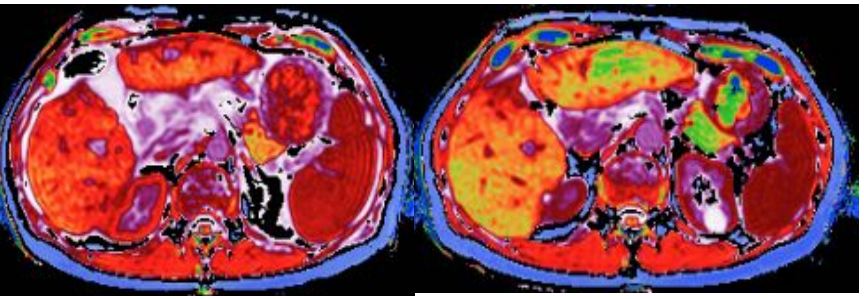
BMI	29.9
ALP	89
GGT	62
ALT	23
AST	28
albumin	39
bilirubin	11
Total serum globulins	27
igg	15.2
platelets	139
Treatment	Azathioprine, Prednisolone
PDFF	2
cT1	821
Age	43

- Liver function tests are not sufficient to assess disease burden
  - UK Multi-Centre AIH Audit Group: ALT normalization does not predict outcomes.
- Patient A: biochemical remission and no significant fibro-inflammation on imaging – quiescent disease
- Patient B: biochemical remission and significant fibro-inflammation on imaging – clinically sub-active disease

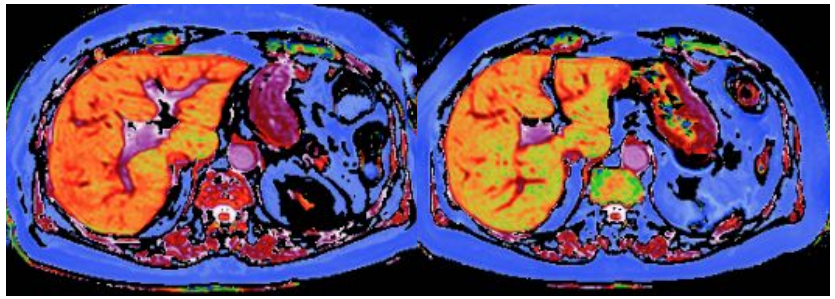
Heneghan et al 2022 eClinicalMedicine

cT1 as a biomarker for therapeutic response in AIH

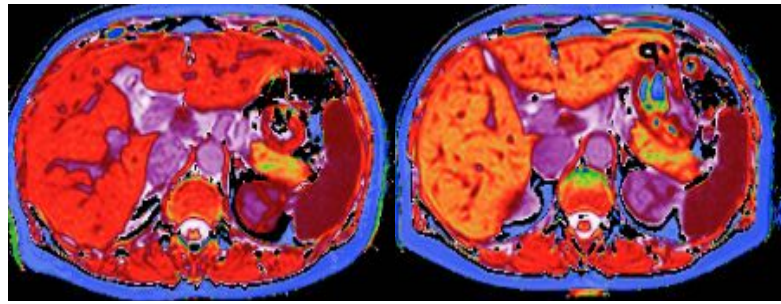
Providing a non-invasive way to monitor patient from diagnosis



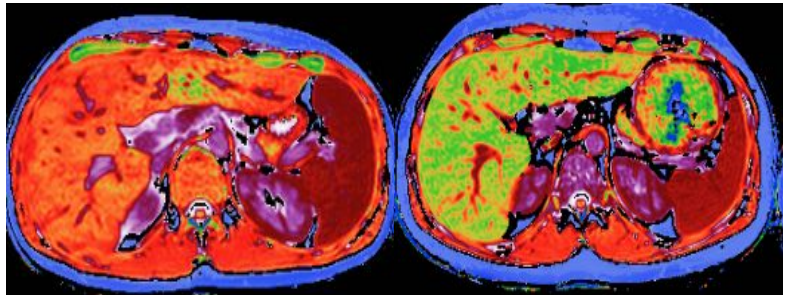
	Baseline	Month 1
cT1 (ms)	1051	936
ALT (IU/L)	1089	216
IgG (g/L)	9.4	11.4



	Baseline	Month 1
cT1 (ms)	947	881
ALT (IU/L)	665	83
IgG (g/L)	16.5	8.48



	Baseline	Month 1
cT1 (ms)	1082	948
ALT (IU/L)	415	74
IgG (g/L)	31	25.8



	Baseline	Month 1
cT1 (ms)	931	807
ALT (IU/L)	469	37
IgG (g/L)	18.6	9.24

Baseline: 48hrs post diagnosis

Summary

- Assessment of treatment response
  - Providing a non-invasive way to assess the effect of a new therapy
  - Utility as trial endpoints alongside IgG/Transaminase's resolution
- Stratification
  - Quiescent vs active disease
- Assessment of disease heterogeneity
  - Non-invasive assessment of disease patchiness
- Identification of sub-clinically active disease
  - Patient most likely to have a flare

"As a patient who has experienced liver biopsy and as an advocate representing the interests of liver patients, **I cannot overstate the importance of developments in non-invasive testing** for liver diseases"

Donna Cryer, President and CEO,
Global Liver Institute