Multi-parametric MRI as a composite biomarker for high-risk NASH

Dimitar Tonev

Perspectum Diagnostics
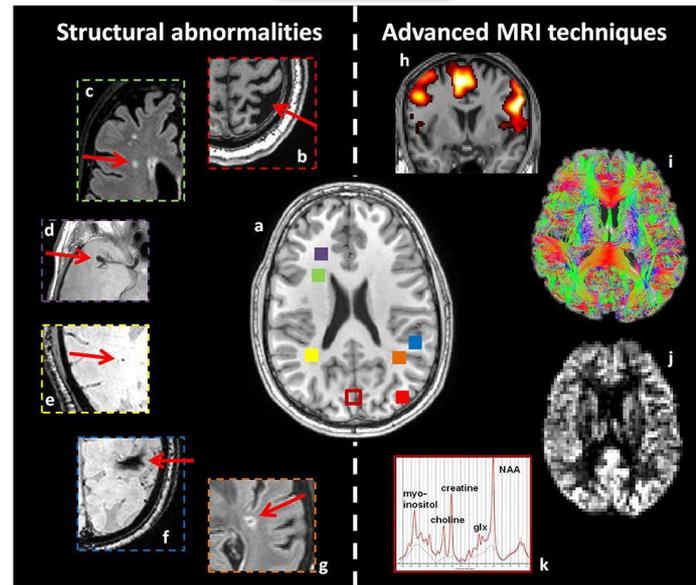
Part 1: An Introduction to Multiparametric MRI and cT1
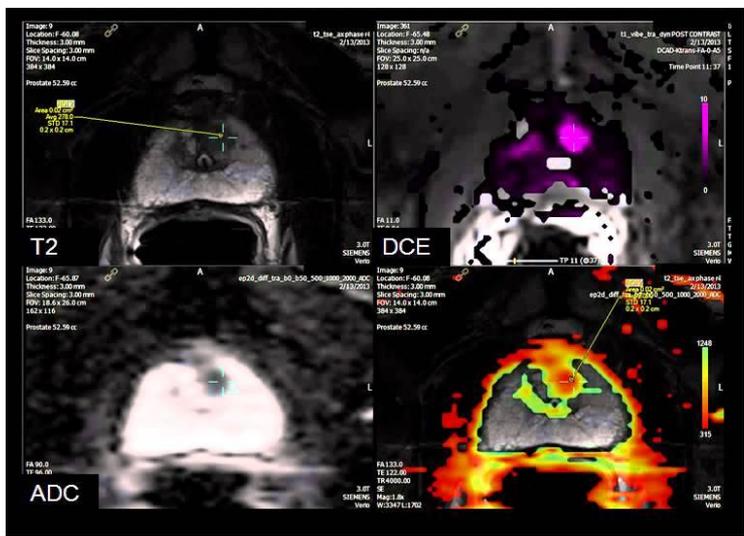
Diagnosi | **Research** | **Guiding biopsy** | **Monitoring**
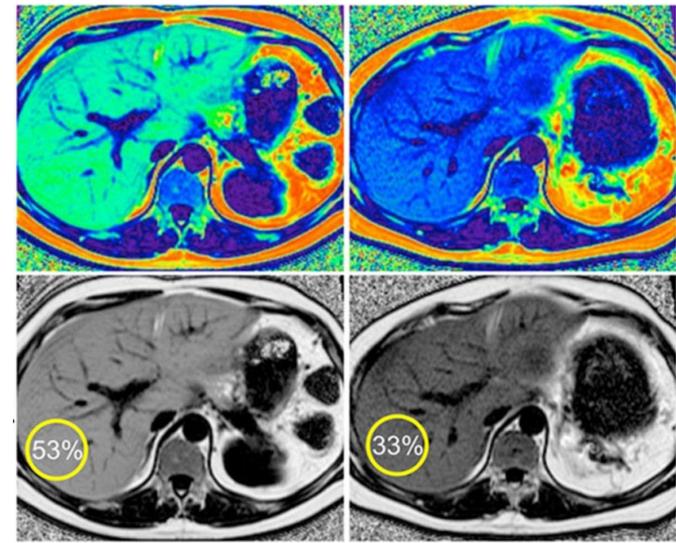
Multiparametric MRI in the liver

T2*

Measured in seconds

Iron

PDFF

Measured as a %

Fat

T1

Measured in seconds
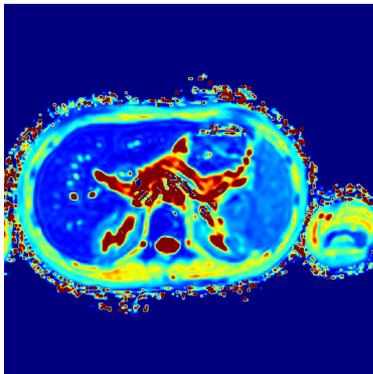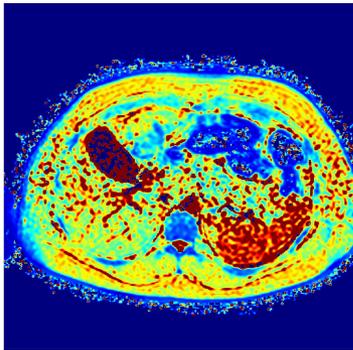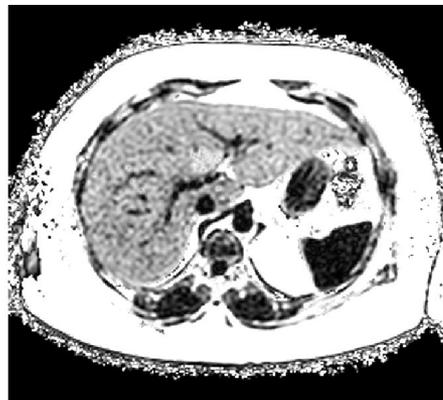
Inflammation and fibrosis

Multiparametric MRI in the liver

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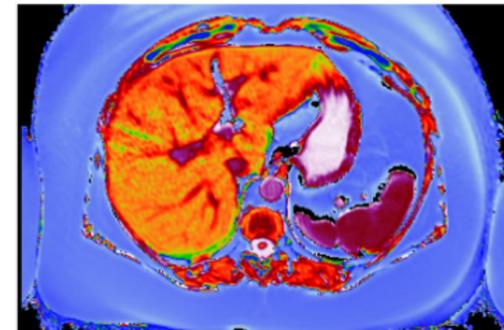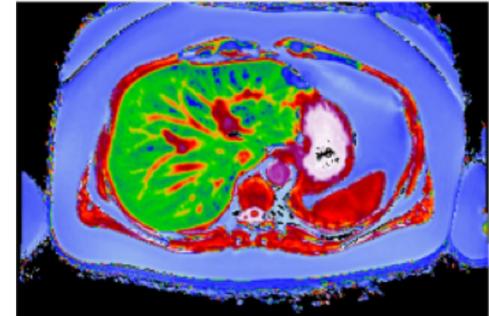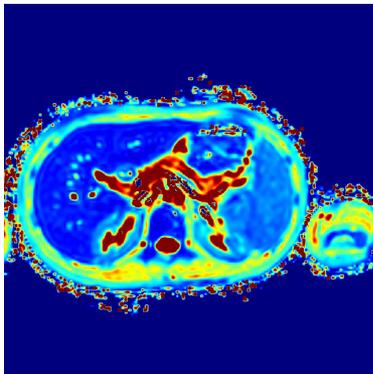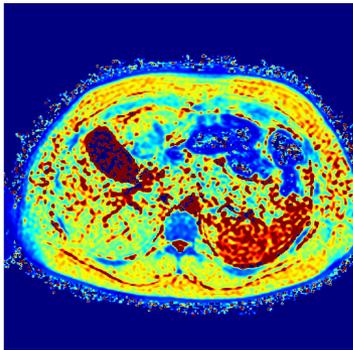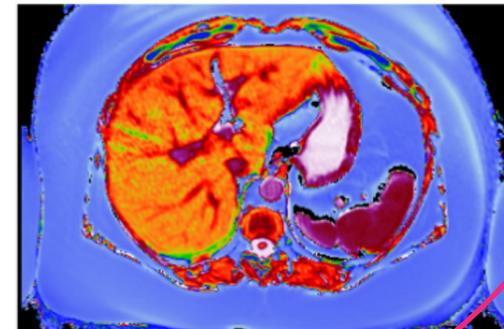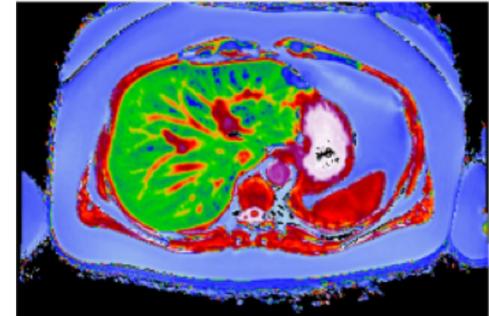**T1**

Measured in seconds

Inflammation and fibrosis

T1 quantification in Cardiac MRI

- **An MRI parameter relating to water molecules and the surrounding structures**

- **Myocardial T1 is a routine component of cardiac MRI examinations and has largely replaced biopsy**

- **T1 is sensitive to a range of cardiomyopathies including, myocardial edema, inflammation, fibrosis and iron**

- **T1 can detect longitudinal changes in disease**

T1-relaxation

Healthy tissue   Interstitial fibrosis
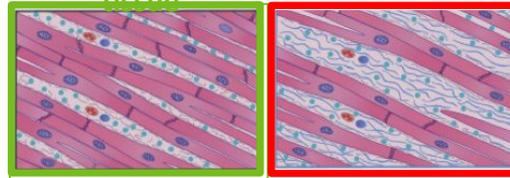
Short T1   Long T1

Diffuse fibrosis
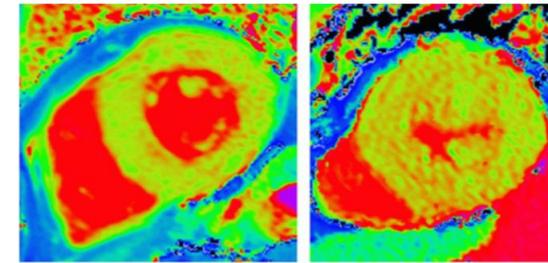
Bull et al, Heart, 2013, 99

Myocarditis
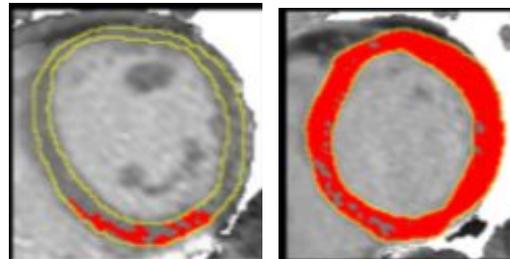
Ferreira et al, J Cardiovascular Med, 2014, 16

Sensitive to change

T1 Maps
Admission   Follow-up   H & E
Native T1: 1091 ms   Native T1: 928 ms
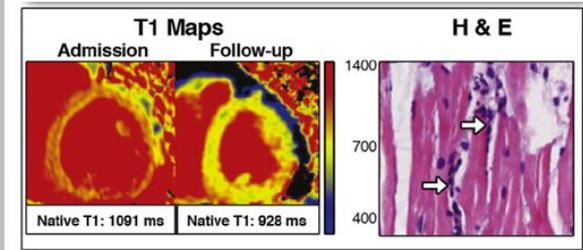
Biesbroek et al, Eur Heart J (2015)

T1 quantification in Liver MRI

T2* iron

T1
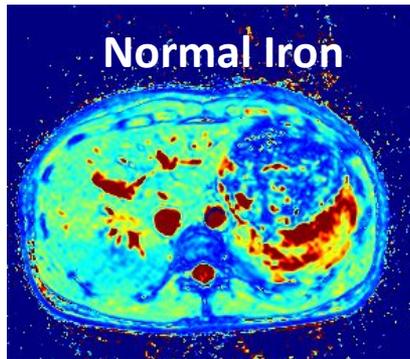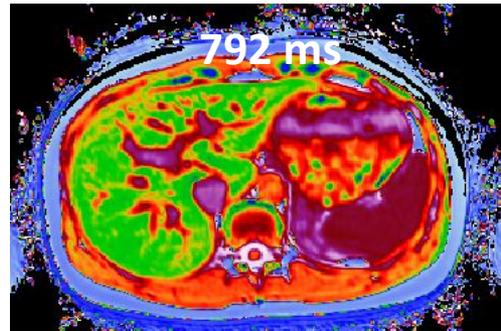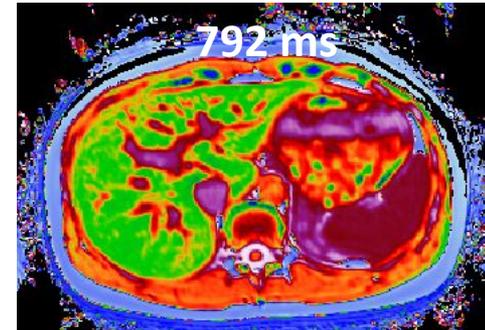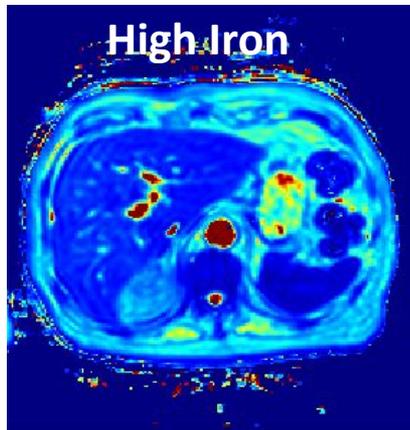
T1 quantification in Liver MRI
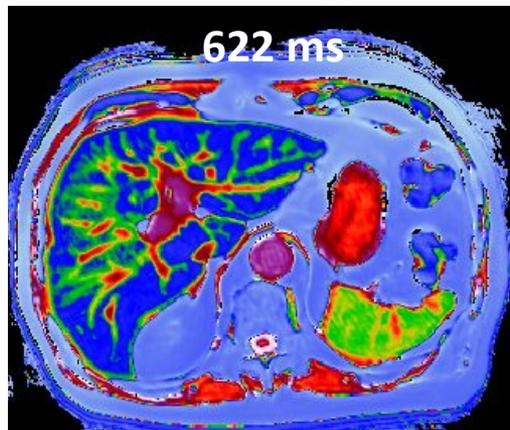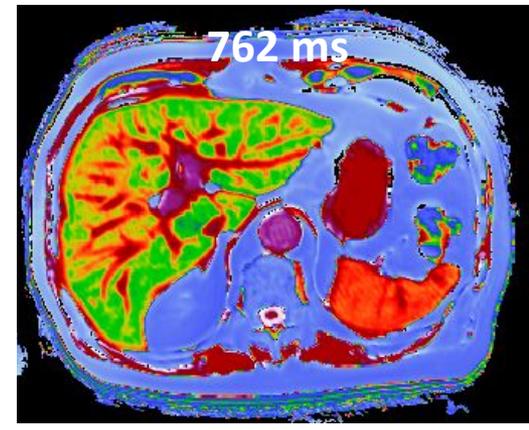
Iron overload (dry weight ≥ 1.8mg.g^{-1}) is prevalent in 4.9% UK biobank population. McKay et al (2017). ASSLD.

T1 quantification in Liver MRI

- **T1 in Liver MRI reported after correcting for iron (cT1)**

- **cT1 is sensitive to liver fibrosis, ballooning and inflammation**

- **cT1 can detect longitudinal changes in fibro-inflammation conditions (e.g. following 6 months antiviral treatment for HVC)**

Fibrosi

(Banerjee et al, 2013)

Balloonin g

(Pavlides et al, 2016)

Inflammatio n

(Pavlides et al, 2016)

Sensitive to change

(Jayaswal et al, 2017)
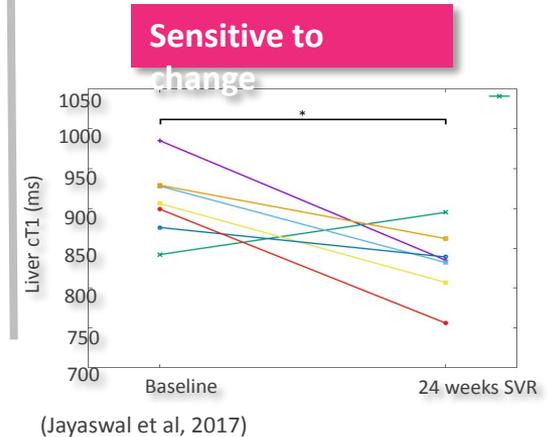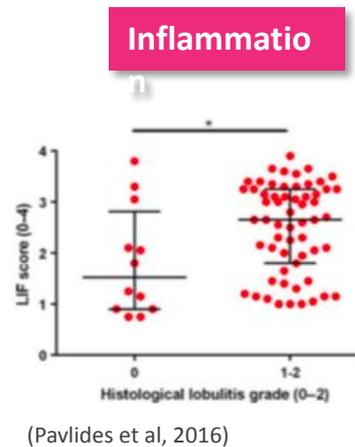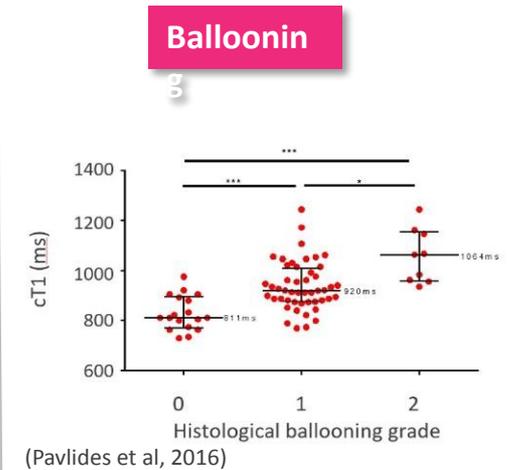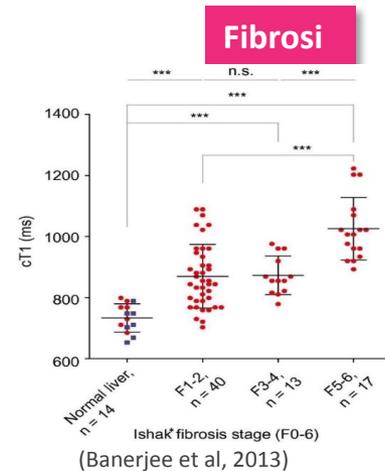
T1 quantification in Liver MRI

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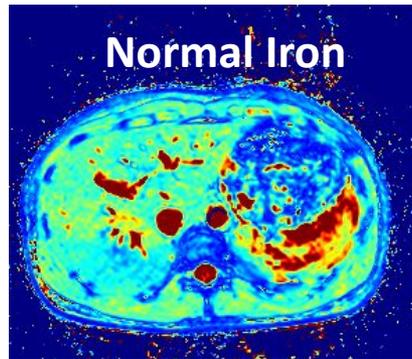
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Sensitive to change

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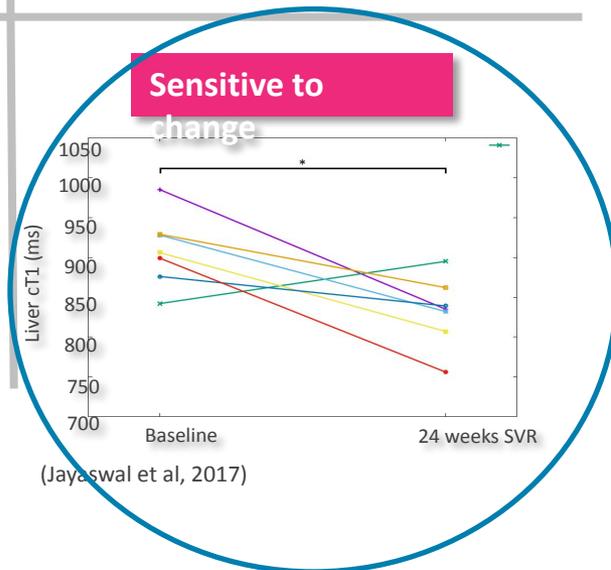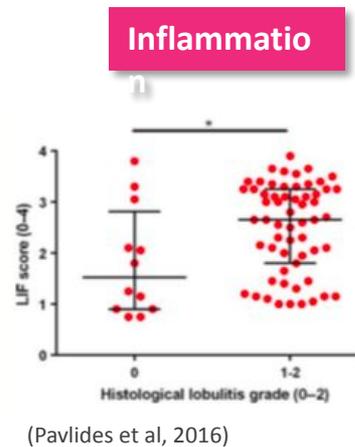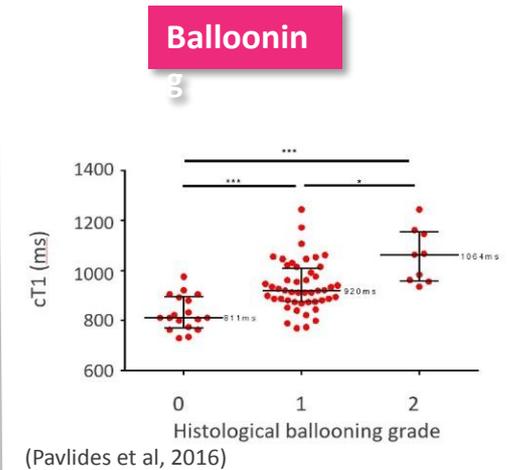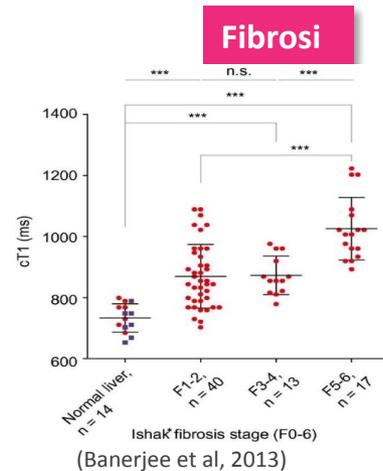
Part 2: Multiparametric MRI as a composite biomarker for metabolic syndrome

Diagnosing Metabolic Syndrome, NAFLD and NASH

- Metabolic Syndrome (MetS) and Fatty Liver Disease is a major epidemic, with UK Biobank work demonstrating that 1 in 3 have high liver fat levels[1].

- Accurate stratification of NAFLD and NASH is essential for effective patient management.

- MRI-PDFF accurately measures steatosis, whereas MRI-cT1 has demonstrated utility in other NASH hallmarks (ballooning, inflammation, fibrosis)

- We explore the utility of these MRI metrics alone and in composite for the identification of NASH and NASH with fibrosis.
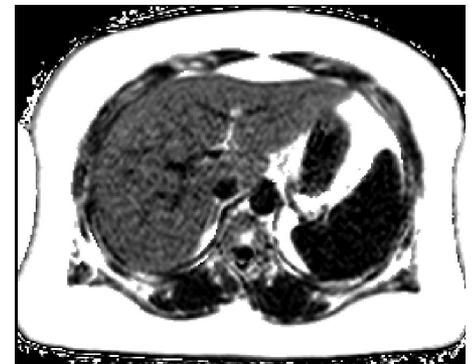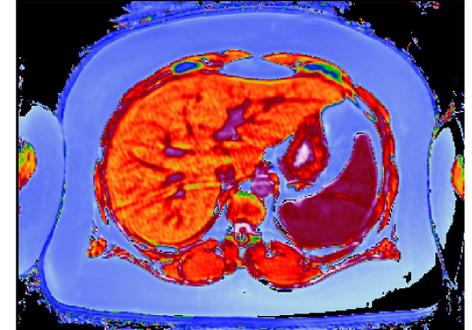
1. Wilman et al (2017). Characterisation of liver fat in the UK Biobank cohort. *PLOS ONE.* 12(4): e0176867

Our Methodology

- 77 individuals with biopsy confirmed NAFLD were included; mean age = 49.4 (18-74), 39% female, 68% BMI ≥ 30.

- All had multiparametric MRI (Liver*MultiScan*™), measuring cT1 and PDFF as well as separate fasting blood glucose measurements.

- We evaluated the ability of Liver*MultiScan* to identify individuals with NASH (NAS ≥ 4) and advanced NASH (NAS ≥ 4 & Brunt Fibrosis ≥ F2).

- Logistic regression analyses were used to derive the diagnostic value of cT1 when used in composite.

Detecting NASH (NAS ≥ 4) with Liver*MultiScan* ™

Liver*MultiScan* cT1 and PDFF both perform well in the detection of NASH

NAS ≥ 4

cT1 optimal cut-off = 866ms

— cT1 0.81 (0.7-0.91)

NAS ≥ 4

PDFF optimal cut-off = 11.7%
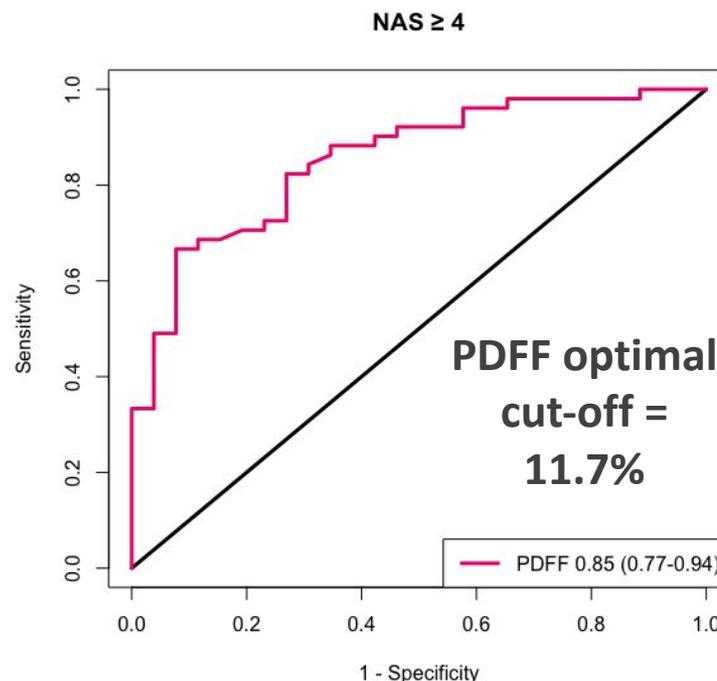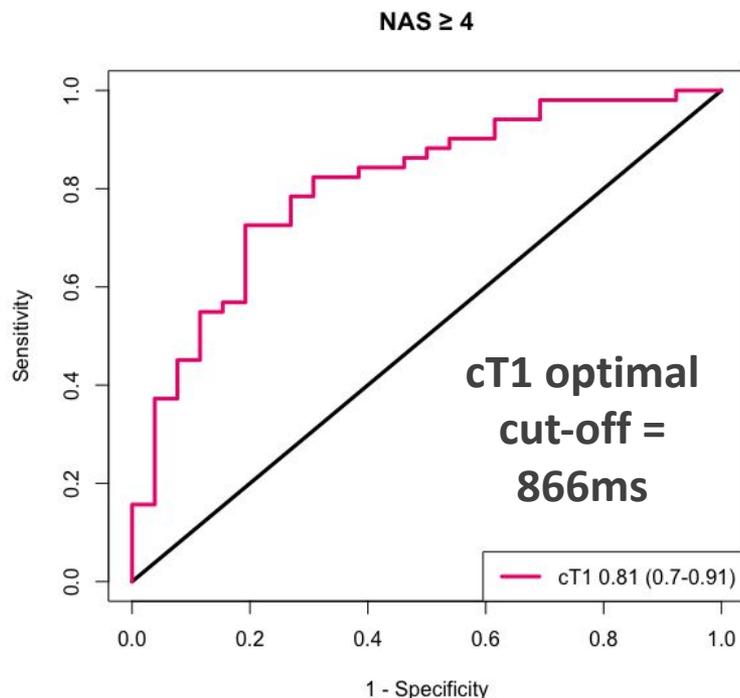
— PDFF 0.85 (0.77-0.94)

Marker	AUROC	Se.	Sp.	PPV	NPV
cT1	0.81 (0.70-0.91)	0.72	0.81	0.88	0.60
PDFF	0.85 (0.77-0.94)	0.67	0.92	0.94	0.59

Detecting NASH (NAS ≥ 4) with Liver*MultiScan* ™

Liver*MultiScan* cT1 and PDFF both perform well in the detection of NASH

NAS ≥ 4

cT1 + PDFF

comb_cT1PDFF 0.88 (0.81-0.96)
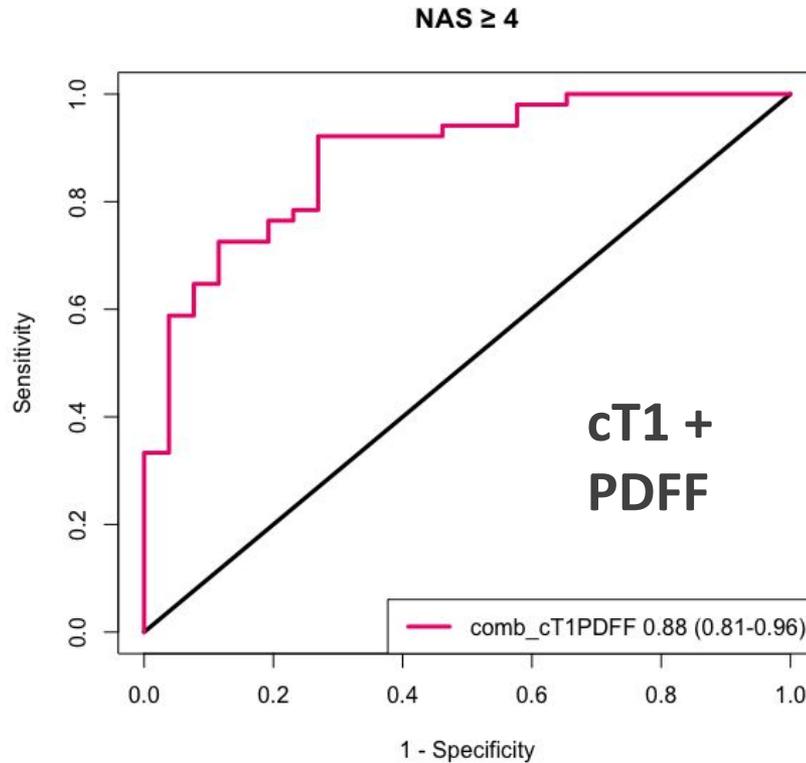
PDFF and cT1 perform well alone for NASH detection, but <u>performance is further improved when the two are used in composite</u>; Composite AUROC = 0.88. (cT1 = 0.81, PDFF =0.85)

	AUROC	Se.	Sp.	PPV	NPV
cT1 & PDFF	0.88 (0.81-0.96)	0.92	0.73	0.87	0.83

Detecting NASH (NAS ≥ 4) with Fibrosis (≥ F2) with Liver*MultiScan*™

In advanced NASH with fibrosis, cT1 outperforms PDFF

NAS ≥ 4 & F ≥ 2

cT1 optimal cut-off = 853ms

— cT1 0.78 (0.68-0.89)

NAS ≥ 4 & F ≥ 2

PDFF optimal cut-off = 9.6%
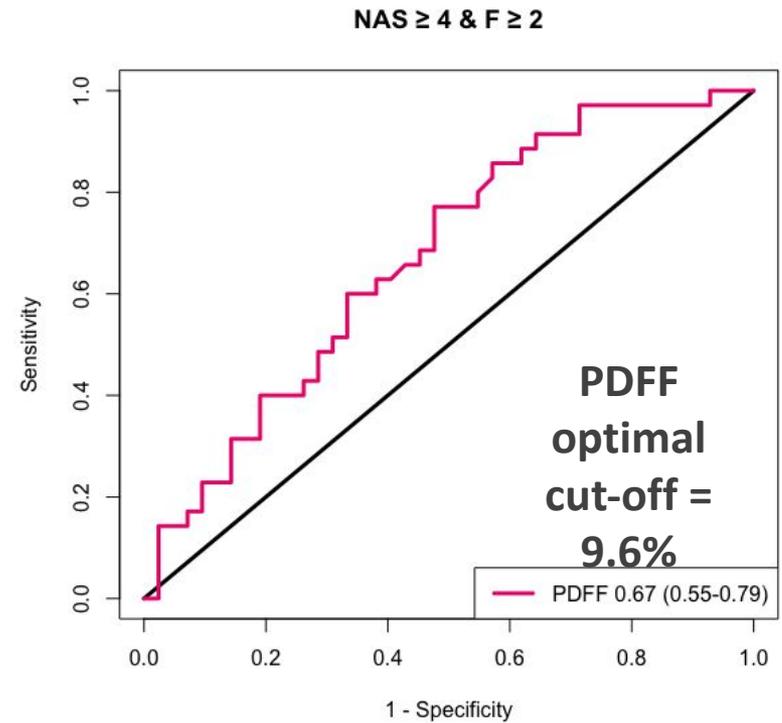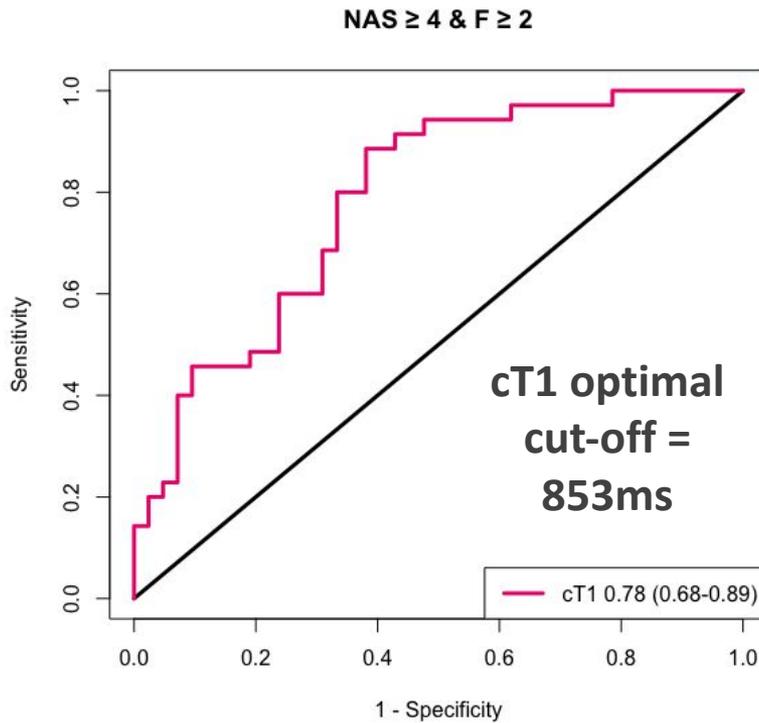
— PDFF 0.67 (0.55-0.79)

Marker	AUROC	Se.	Sp.	PPV	NPV
cT1	0.78 (0.68-0.89)	0.89	0.62	0.66	0.87
PDFF	0.67 (0.55-0.79)	0.78	0.52	0.57	0.73

Liver*MultiScan*™ cT1 + Glu. for NAS ≥ 4 & ≥ F2

NAS ≥ 4 & F ≥ 2

cT1 + glu.

comb_cT1_glu 0.89 (0.81-0.96)
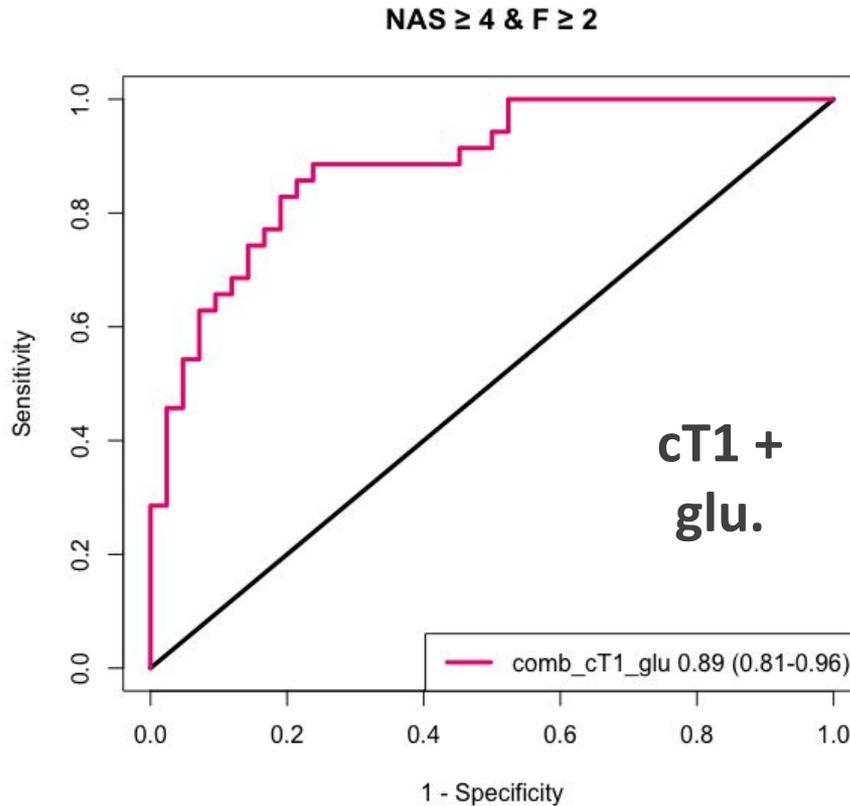
cT1 performed well alone in the detection of NASH cases with fibrosis, but **superior performance is achieved when cT1 is used in composite with glu.**; Composite AUROC = 0.89, cT1 = 0.78

	AUROC	Se.	Sp.	PPV	NPV
cT1 & Glu.	0.89 (0.81-0.96)	0.89	0.76	0.76	0.89

Conclusions

- PDFF and cT1 are effective tests for identifying patients with NASH, with performance improved further when used in composite.

- cT1 retained high utility for identifying NASH patients with fibrosis, whereas PDFF does not perform as well.

- The performance of cT1 for identifying NASH patients with fibrosis improved further when used in composite with fasting glucose (AUROC = 0.89).

- Multiparametric MRI (Liver*MultiScan*™) measures both PDFF and cT1 and so could have an important role in aiding physician assessment of a wide spectrum of NAFLD patients.