Perspectum Diagnostics

Challenges in clinical trials for liver disease

See what we measure

EXECUTIVE SUMMARY

Bringing new therapeutics to market safely and efficiently requires reliable biomarkers for measuring efficacy and enriching clinical trials. For liver conditions such as non-alcoholic fatty liver disease (NAFLD), the lack of accurate, reliable and affordable quantitative measures is a critical rate-limiting step in the development of urgently-needed treatments.

Liver biopsy remains the only definitive diagnostic for staging and monitoring of fatty liver disease. This presents several unique challenges for clinical trial design, including recruitment of patients and selection of appropriate primary and secondary outcome measures, to monitor treatment and determine therapeutic efficacy. As early liver disease is often asymptomatic, differentiating those patients who will progress to clinically-relevant liver disease is a further challenge.

Liver*MultiScan* is an MR-based imaging non-invasive tool, that has attained CE-marking and FDA clearance to aid the diagnosis of patients with chronic liver disease.

Liver*MultiScan* Discover, for clinical trial use, can characterise liver tissue in **three** ways, providing accurate measurements of **liver fat**, **hepatic iron** content and **fibro-inflammatory disease**, using the proprietary Liver Inflammation and Fibrosis (LIF) score. The LIF score has been shown to stratify NAFLD and NASH patients, correlate with histological markers of inflammation and fibrosis, and predict liver-related outcomes.

Available as a Quantitative Analysis Service, Liver*MultiScan* Discover offers a standardized and high quality method for supporting the diagnosis and monitoring of the liver for both observational and interventional studies.

CHALLENGES IN CLINICAL TRIALS FOR FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) is a condition of increasing prevalence, estimated to affect 30% of Western populations (Bellentani, et al., 2010). NAFLD encompasses a range of disorders from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis. Identifying individuals at greatest risk of progression remains a major unmet need both in diagnosis and management of NAFLD.

Definitive staging of fatty liver disease requires an invasive liver biopsy, to obtain a histological grading of the degree of steatosis, inflammation and fibrosis. While liver biopsy remains the gold standard diagnostic for NASH, the high cost, inherent risk and poor accuracy of this invasive diagnostic test are widely recognised limitations (Castera & Pinzani, 2010; O'Shea, et al., 2010). This poses several challenges for clinical trials involving fatty liver disease:

1. *Screening* - Candidates must be identified from the general at-risk population to be considered for an interventional study. Fewer than 25% of US healthcare providers are routinely performing liver biopsies in patients with suspected NAFLD, and this is often restricted to patients at end-stages of disease, where treatment options are limited (Rinella, et al., 2016).

2. *Enrichment* - Disease activity must be reliably and accurately staged, prior to enrollment. Patients are often anxious and discouraged by the requirement for a research biopsy resulting in an up to 80% chance they will not enroll in the study. Further, some therapeutic agents work best at early stages of disease, others at later stages. Strategies to engage patients with interventional clinical trials, and to enrich the patients who enroll for the type of fatty liver disease the intervention is most likely to be efficacious in, are needed.

3. *Measuring Change* - Repeated liver biopsies are restricted by institutional review boards to a minimum interval of six months, which is a critical rate-limiting step for drug development programs. Accurate, reliable and affordable non-invasive tests that (i) provide **biomarkers** for disease activity, (ii) can safely monitor **early therapeutic efficacy** and (iii) can act as a **surrogate endpoint**, need to be exploited.

LIVER*MULTISCAN*: MULTIPARAMETRIC MRI FOR CLINICAL TRIALS

With an estimated 4,500 biopsy-confirmed NASH patients required to fill clinical trials in the next year (Harrison, 2015), innovative non-invasive solutions are urgently required. Both the EMA and FDA currently support the inclusion of non-invasive liver tests (NILTs) in clinical programs for NAFLD and NASH, in addition to independent biomarker qualification programs for individual NILTs. Liver*MultiScan* is a recently developed approach for the non-invasive assessment of liver diseases that brings multiparametric MR imaging to the forefront of liver disease management. Liver*MultiScan* has been FDA 510(k) cleared to aid diagnosis of early liver disease with high accuracy and reproducibility, enabling quantitative tissue characterization, ideal for longitudinal monitoring. Multiparametric MRI is used as the definitive liver assessment in 2 of the 3 largest liver studies currently enrolling, offering state-of-the-art solutions to improve screening, enrichment and efficacy indications for chronic liver disease **(FIGURE 1).**

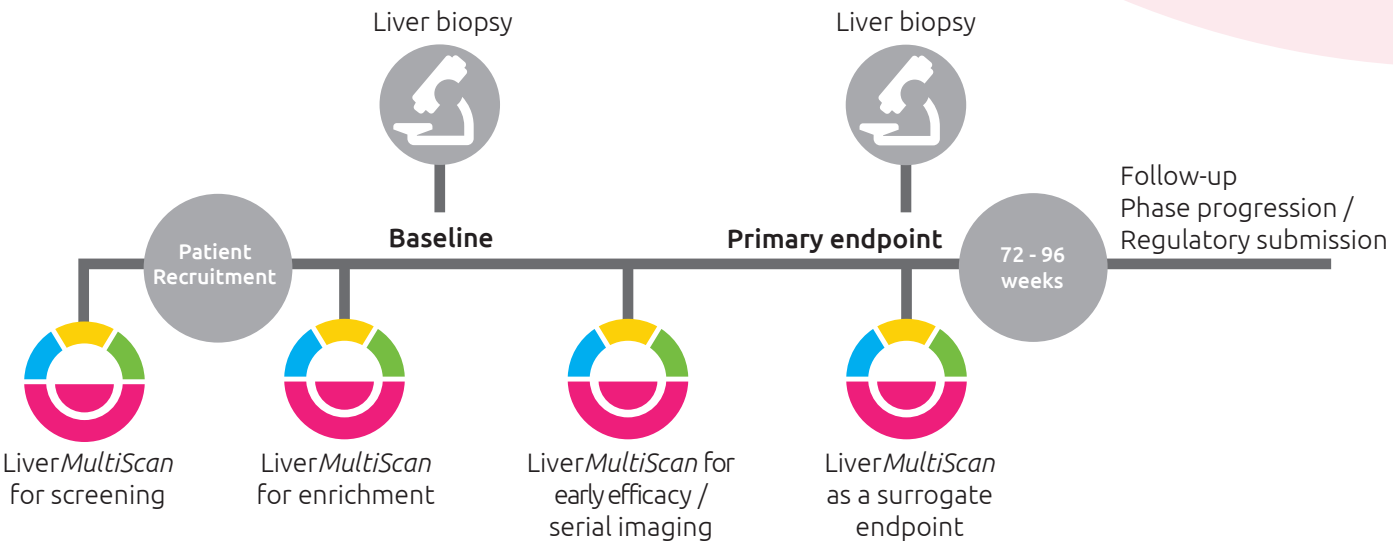


FIGURE 1 Schematic illustrating the multiple points at which Liver*MultiScan* Discover can be used in the clinical trial pathway

HOW DOES LIVER*MULTISCAN* WORK?

Liver*MultiScan* is a software platform that enables post-processing of Magnetic Resonance Imaging (MRI) data into parametric maps. Unlike ultrasound or MR-based elastography techniques, which attempt to provide an indication of hepatic fi brosis by measuring the mechanical properties of liver "stiffness", Liver*MultiScan* uses MRI mapping techniques to characterize liver tissue at the cellular level, delivering quantification of liver fat, iron load and fibroinflammatory disease using Proton Density Fat Fraction (PDFF), T2* and T1 maps, respectively.

Liver*MultiScan* is unique in that it corrects for the interdependencies of these MR signals. In patients with increased hepatic iron, alternative MR assessments, such as MR elastography, suffer due to low signal, which can result in inadequate visualization of shear waves. Similarly, without considering the effect of iron, measurements of T1 are inaccurate (leading to misclassification) in a substantial proportion of patients (Venkatesh, et al., 2013; Hoad, et al., 2015).

Perspectum's proprietary modeling algorithms correct for the degree of iron overload, yielding a corrected T1 value (cT1). cT1 can be mapped onto a scale of 0-4, called the Liver Infl ammation and Fibrosis (LIF) score. Clinical studies have shown that the LIF score/cT1 **correlates with histological markers** of inflammation and fibrosis (Banerjee, et al., 2014) **(FIGURE 2)**, **stratifies NAFLD and NASH patients** (Pavlides et al., 2015), and **predicts liver-related outcomes** (Pavlides et al., 2016).

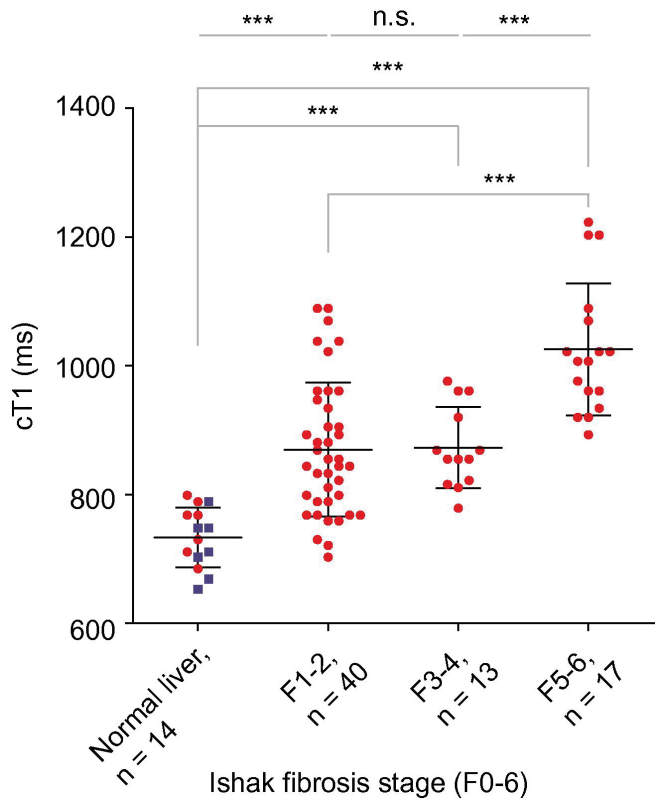
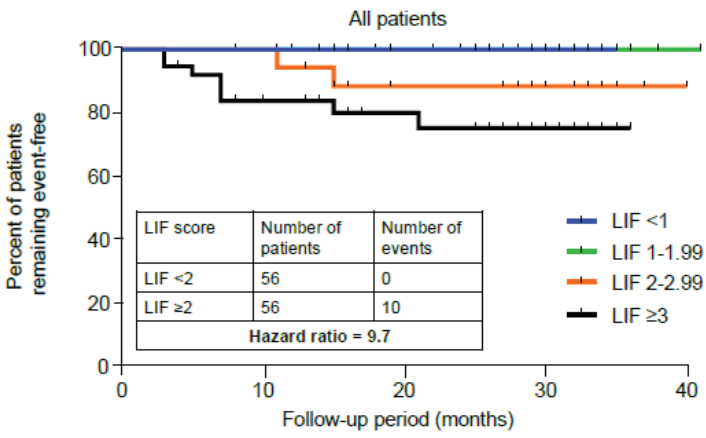


FIGURE 2 A prospective study of 79 patients undergoing liver biopsy compared to MRI. The corrected T1 measure correlated strongly with histology (rs = 0.68, p <0.0001 for fibrosis), with an area under the receiver operating characteristic curve (AUROC) of 0.94 for the diagnosis of any degree of fibrosis. Figure taken from Banerjee et al., 2014, Journal of Hepatology.

THE LIF SCORE PREDICTS CLINICAL OUTCOMES

In a prospective clinical study, 112 patients with chronic liver disease were recruited for MR imaging and followed for a median of 27 months. Medical records review revealed that the development of liver related clinical events occurred only in patients with an initial LIF score of ≥2, with no events in any patients with a LIF score <2 (100% negative predictive value (NPV) at LIF cut-off =2; Pavlides et al., 2016) **(FIGURE 3)**.



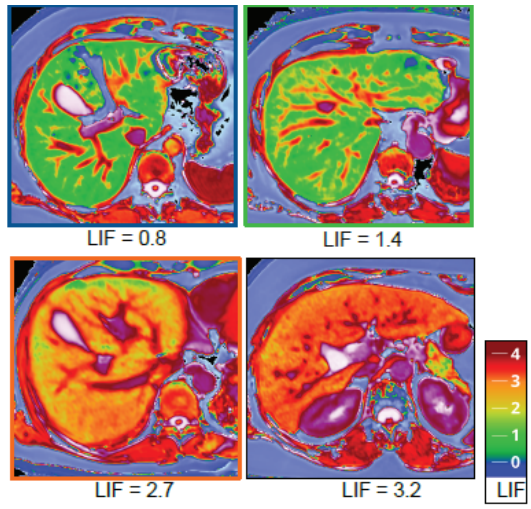


FIGURE 3 LIF ≥ 2 predicts clinical outcomes. Figure taken from Pavlides et al, 2016, Journal of Hepatology. MRI data from a Siemens 3T scanner processed using Liver*MultiScan* Discover .

MEASURING FAT – PROTON DENSITY FAT FRACTION (%)

Liver fat is quantified using state-of-the-art proton density fat fraction (PDFF) calculations, which exploit the chemical-shift in water and fat separation to estimate hepatic fat concentration. PDFF offers an MR-based biomarker that can be readily standardized across MR platforms, scanners and field strengths to provide a reproducible and robust measure of liver fat. Unlike ultrasound or CT, which is limited to the detection of extensive steatosis, MRI has been widely validated as the most reliable method for quantifying fatty liver disease (Idilman, et al., 2013).

Unlike traditional Magnetic Resonance Spectroscopy (MRS) which is subject to the limitation of single-voxel acquisition, PDFF provides a map of whole liver from a single breath hold. Unlike transient elastography, which has technical limitations in patients with obesity and ascites (Talwalkar, 2008; Carlson, et al., 2009) Liver*MultiScan* can be used to analyze MRI data in any patient, irrespective of body size. Hepatic fat content is measured by 3 point DIXON or IDEAL (iterative decomposition of water and fat with echo asymmetry and least squares estimation (Reeder, et al., 2007).

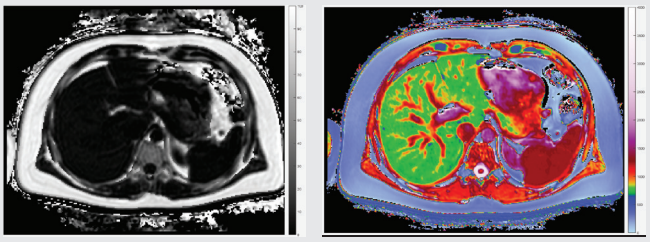
MEASURING IRON – T2* (MG/G)

Iron overload is quantified using a T2* map, which is one of the MR relaxation parameters. Its value is heavily influenced by disturbances in the local magnetic field, such as those caused by the presence of iron. T2* is used as a biomarker in the assessment of hepatic iron overload, or hemosiderosis (Hoad, et al., 2015) and is used to obtain the corrected T1 measure.

MEASURING FIBROSIS AND INFLAMMATION - CORRECTED T1 (MSEC) & THE LIF SCORE

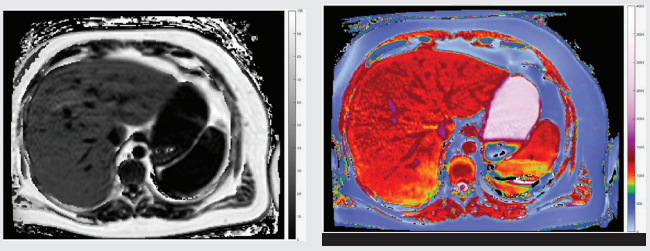
T1 (another important MR relaxation parameter) has been used as a biomarker for the assessment of myocardial inflammation and fibrosis (Moon et al., 2013), and is an emerging technique for rapid quantification of hepatic fibro-inflammatory disease (Banerjee, et al., 2014; Pavlides et al, 2015; Cassinotto, et al., 2015; Hoad, et al., 2015). T1 is affected by how tightly bound the water protons are and is essentially a surrogate measure of free water in the tissue. Free water, and therefore T1, increases with fibrosis and inflammation. However, T1 is also affected by the presence of iron and this effect must be corrected for (corrected T1, or cT1). The cT1/LIF score are scanner-, field strength- and vendor-independent, allowing standardization of this measurement across different MRI systems and sites.

CASE STUDY 1 NAFLD: SIMPLE STEATOSIS



Male, BMI of 29, with suspected non-alcoholic fatty liver disease (NAFLD). Liver*MultiScan* measures liver fat of 5% and a LIF score of 0.8 (cT1 of 770ms; upper limit of normal = 822ms). Biopsy shows mild steatosis (Brunt grade 1/3), minimal inflammation (Lobular inflammation 1/3, Ballooning 0/2, NAFLD Activity Score 2/8), with no fibrosis. †

CASE STUDY 2 NASH: STEATOHEPATITIS



Male, BMI of 31, with suspected NASH. Liver*MultiScan* measures liver fat of 17% and a LIF score of 3.7 (cT1 of 1197ms; upper limit of normal = 822ms). Biopsy shows moderate steatosis (Brunt grade 2/3) and moderate to severe inflammation (Lobular inflammation 2/3, Ballooning 2/2, NAFLD Activity Score 6/8) with bridging fibrosis (Kleiner fibrosis stage 3/4). †

† Images courtesy of Dr P Eddowes and Dr G Hirschfi eld, Centre for Liver Research and National Institute for Health Research, Birmingham Liver Biomedical Research Unit, University of Birmingham, UK

ACCELERATED RECRUITMENT WITH HIGH THROUGHPUT MR IMAGING AS A SCREENING TOOL FOR NASH

Lengthy timelines have been cited as one the primary obstacles to conducting clinical trials in the United States (U.S. Department of Health and Human Services; (Sertkaya, et al., 2014)). Patient recruitment requires a substantial investment of time and money, and failure to recruit can cause costly delays or trial cancellation, wasting resources. In addition, for conditions such as fatty liver disease, an initial diagnosis of NAFLD is often based on incidental observation – such as high blood values for alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or on ultrasound examination due to non-specific abdominal pain. There is increasing competition for limited patient pools as the number of new therapeutics advancing to first-in-man studies continues to rise.

One approach to accelerating study enrollment is to run a multi-center study, reducing the burden on individual sites and enabling recruitment to run in parallel. Not considering the inherent variability introduced in the data collection and analysis, this approach for risk reduction comes at significant financial cost to the study coordinator, with recruitment, retention, project and data management costs levied on a per site basis, in addition to the increased administrative, monitoring and logistical costs and burdens for multi-site studies (Sertkaya et al., 2014).

Liver*MultiScan* has been competitively selected as the only liver imaging tool for a large UK-based population study, the UK Biobank, which will scan 100,000 volunteers over 5 years, at a maximal rate of 51 patients per day across three sites. Results of the first 1,000 volunteers were presented at the AASLD Annual Liver Meeting in 2015 (Kelly & Banerjee, 2015). 97% of datasets reported LIF and fat fraction data successfully. 17.8% of the population had a PDFF greater than 5%, in agreement with UK estimates of steatosis (Preiss & Sattar, 2008).

Patients can be stratified based on their LIF score by introducing Liver*MultiScan* to screen at-risk populations for NASH (see **FIGURE 4**, below). These include: well-characterized NAFLD/NASH cohorts at academic centers, diabetic registries, patient-facing organizations (e.g. Chronic Liver Disease Foundation), and primary care networks. High-throughput MR imaging has been shown to be cost-effective in identifying patients with NASH.

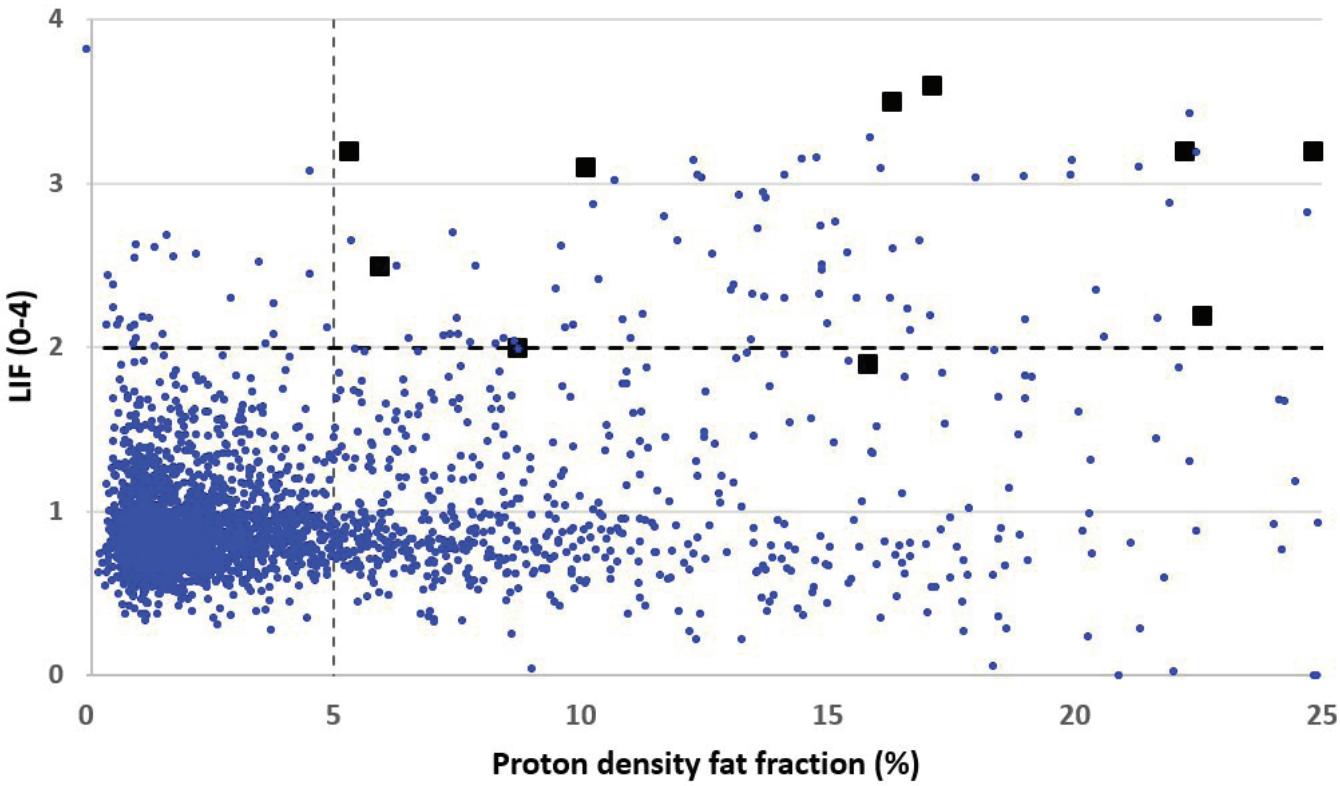


FIGURE 4 LIF vs PDFF in 3,071 unselected (blue dots) subjects from UK Biobank and 10 biopsy confirmed NASH (black squares) populations. **A LIF ≥ 2 and PDFF LIF ≥ 5%** correctly identifies patients with NASH.

SELECTING THE RIGHT NASH PATIENTS FOR TRIAL ENROLLMENT

While conventional clinical trials in fatty liver disease have relied on biopsies for inclusion, potential strategies for enrichment have, to date, been limited to serological markers, such as the NAFLD fibrosis score, FIB-4, BARD score and AST/ALT ratio. These indirect serum marker panels have been shown to be reliable predictors of advanced liver fibrosis (McPherson et al, 2010), but there is a lack of options for detection of early disease.

Currently, a high percentage of patients recruited to a study undergo a research biopsy at a cost of approximately $5,000, but are not allowed to progress in the trial. This is disappointing to patients, their clinicians, trial administrators and sponsors. Recent data has shown that cT1/LIF score can accurately assess NAFLD histological disease severity **(SEE FIGURE 5)**.

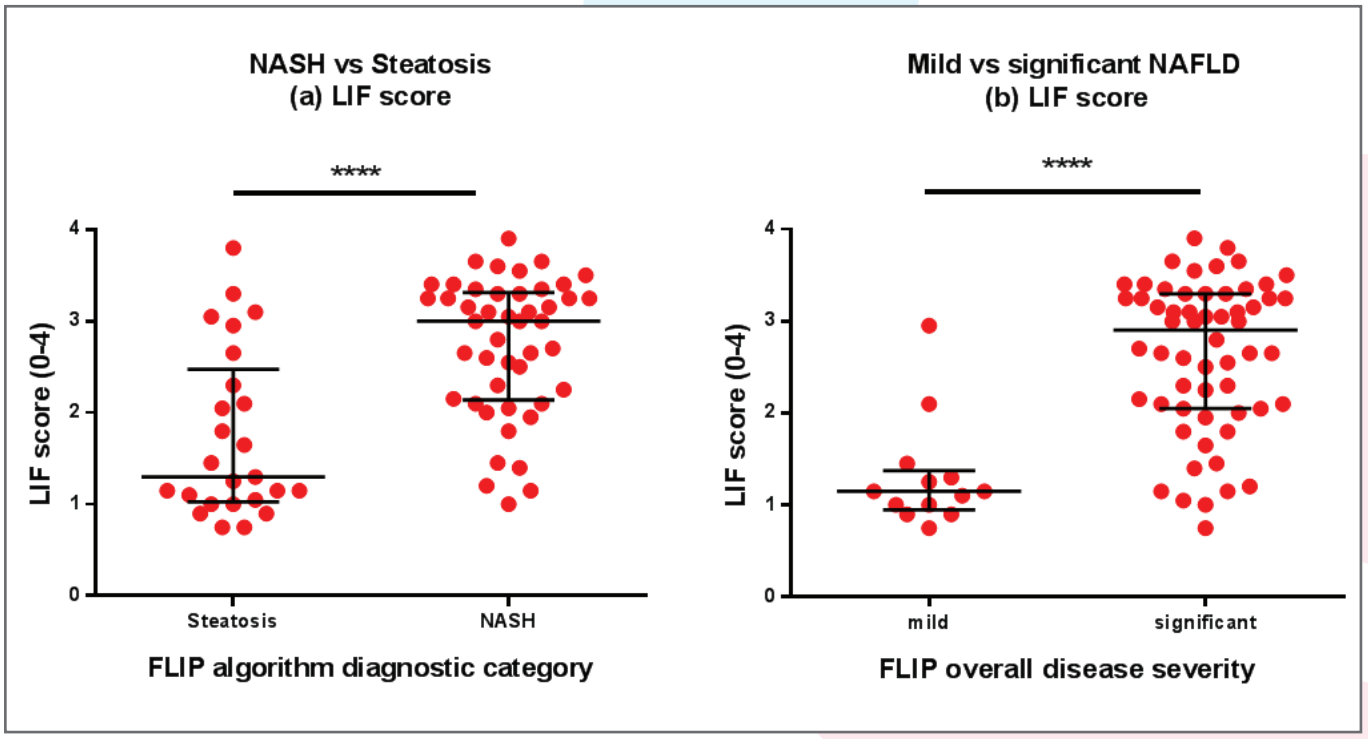


FIGURE 5 - LIF score for NAFLD classification according to the FLIP algorithms. LIF scores are significantly different between (a) patients with simple steatosis and NASH (1.3 vs 3.0; p<0.0001) and (b) patients with mild vs significant overall disease severity (1.2 vs 2.9; p<0.0001). Lines and error bars indicate the median and interquartile range on both graphs. *** p<0.0001. Figure taken from Pavlides et al, 2015, Hepatology.

SCENARIO ANALYSIS - USING LIF FOR ENRICHMENT

The potential benefit of including Liver*MultiScan* can be modeled assuming standard selection criteria for suspected NAFLD, with confirmatory biopsy prior to study enrollment. Using Liver*MultiScan* to screen patients prior to biopsy, the LIF score can enrich the population up to 1.7-fold, screening out unsuitable patients and biasing the sample to identify those patients with a measurable degree of fibro-inflammatory disease and higher likelihood of risk progression. As illustrated in **FIGURE 6** (overleaf), for every 100 patients with suspected NASH – identified according to known risk profiles e.g. high BMI, type-2 diabetes and abnormal liver enzymes – only 16 patients would meet desired enrollment criteria of NAS>4, F2/3 fibrosis. This equates to a total cost of $500,000 for liver biopsies alone. Using steatosis alone, enrichment increases 1.3 fold, but many non-NASH patients with no significant fibrosis will still require confirmatory biopsy, only to be excluded from enrollment. Liver*MultiScan*-phenotyped patients, dependent on trial design, may still require confirmatory biopsies, but with a significant reduction in overall expenditure on unnecessary biopsies by up to 50%. Significant savings will be realized in reduced number of unnecessary biopsies, reduced institution fees, fewer per-site management and administration costs, and accelerated trial progression.

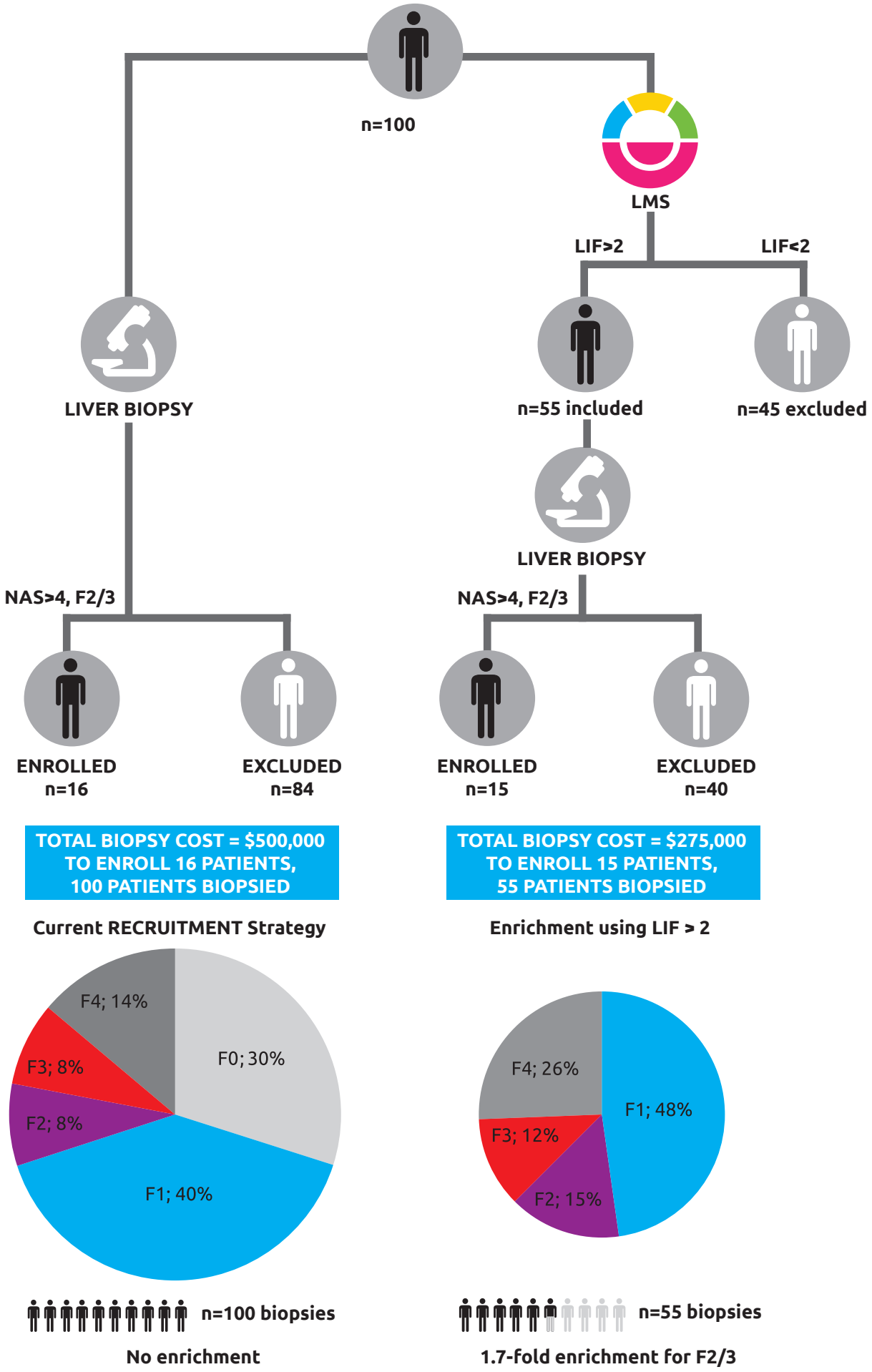


FIGURE 6. For every 100 patients screened, applying a LIF≥2 cut-off will prevent unnecessary biopsies in 45 patients with a 1.7-fold enrichment of F2/3 NASH fibrosis 97% negative predictive value (NPV) and 27% positive predictive value (PPV). This assumes a NASH prevalence of 70% (NAS score ≥ 4), of which 20% are classified as cirrhotic (F4). METAVIR fibrosis stage (F0-4) has been estimated, according to relative distributions observed in in NAS ≥ 4 patients in clinical trials for Liver*MultiScan* (Banerjee et al., 2014, Pavlides et al., 2016.). This analysis assumes a cost of $5,000 per liver biopsy, not including additional trial costs.

MEASURING CHANGE

Successful drug development requires the demonstration of safety, tolerability, and **"clinically meaningful benefits"** as determined by measured improvement in patient survival, feel, or function (Sanyal, et al., 2015). For conditions such as NAFLD, reliance on reduction in liver-related mortality alone has been deemed both impractical and prohibitively expensive, requiring long time-frames to detect change. Moreover, serial evaluation using liver biopsy poses a safety risk, and is unpleasant for patients, affecting clinical trial logistics and completion, and also inflicting pain.

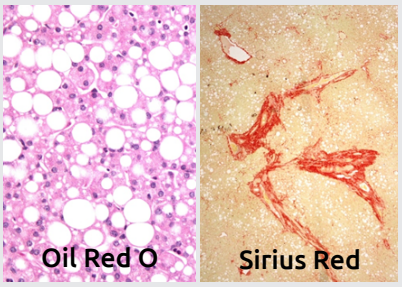
There are no validated patient-reported outcome measures (PROM) for liver disease, and limited data correlating biomarkers with patient outcomes. Several endpoints for early stage disease have been proposed, including development of cirrhosis, improvement in NAFLD activity score or reduction of hepatic steatosis by imaging. Reversal of steatohepatitis with no evidence of progression to advanced fibrosis (stage 3 or 4) has been recommended by the FDA as an acceptable surrogate endpoint for NASH Phase II/III studies (Sanyal, et al., 2015).

The high accuracy, sensitivity and specificity of Liver*MultiScan* offers the potential for a longitudinal analysis of patients, monitoring changes in liver fat, iron and LIF (see **Case Studies 3 and 4**). The test-retest coefficient of variance of Liver*MultiScan*, calculated from repeat scans of healthy volunteers, is 1.75%. In an untrained patient population, this may be up to 5%.

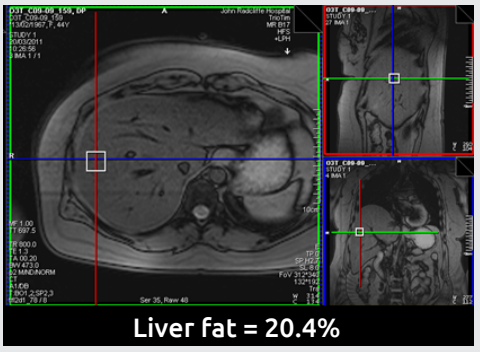
This precision in measurement allows us to reduce the sample size required in a Phase 2/3 study to detect efficacy, translating to a huge cost-saving to the sponsor. To have a 90% chance of detection, with significance level 1%, a decrease in the primary outcome measure from LIF 3 to LIF 2 over time requires 44 trial participants (22 in an intervention group; 22 as placebo-controls). This magnitude of study can be executed within a year at a single center to enable a strategic decision to continue the development of a therapeutic.

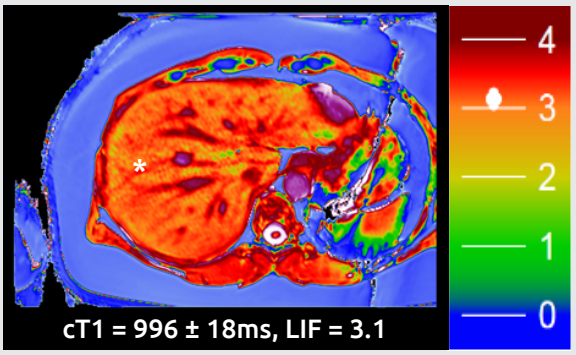
CASE STUDY 3 BARIATRIC SURGERY

A 44-year-old obese female who underwent bariatric surgery in March 2011. Pre-operative BMI was 34.3 with a visceral fat content of 131 cm^2. Liver biopsy taken during her gastric band insertion (* in top right), showed 90% of hepatocytes had lipid inclusions, inflammation and an Ishak score of 3, with marked pericellular fibrosis as well. Hepatic lipid content, measured by MRS, was 20.4% (middle panel). Post-operative BMI, measured 11 months after surgery, was 24.4, with a visceral fat content of 28 cm^2. Post-operative hepatic lipid content, measured by MRS, was 1.7%, showing normalization of liver fat. The corresponding cT1 maps (right- hand panel) showed an improvement in cT1/LIF score, with reduction from LIF = 3.1 to LIF = 0.9, suggesting a resolution of liver inflammation and/or fibrosis. There was no clinical indication to support a follow-up biopsy.



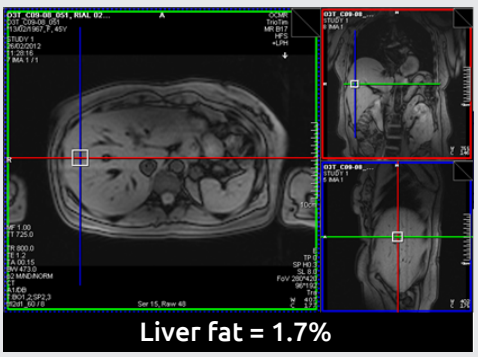
Pre-Treatment

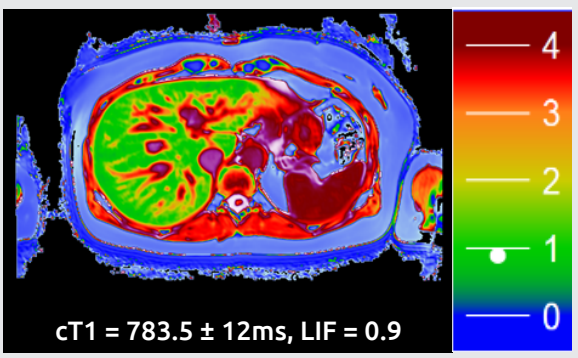




Patient with biopsy-proven NASH, showing pericellular and bridging fibrosis responding to bariatric surgery and weight loss with resolution of hepatic steatosis and LIF score.

Post-Treatment

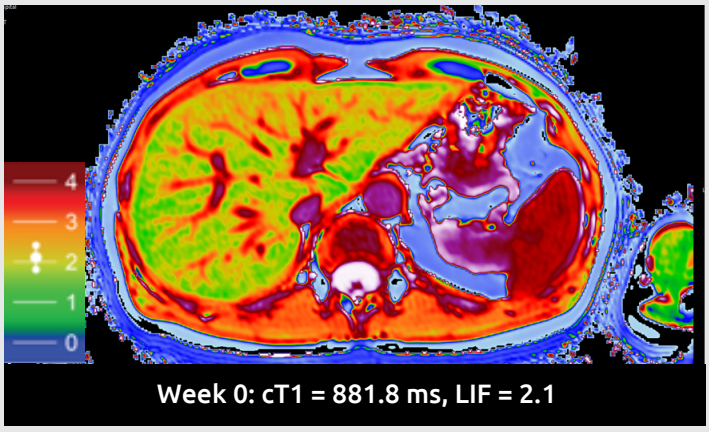




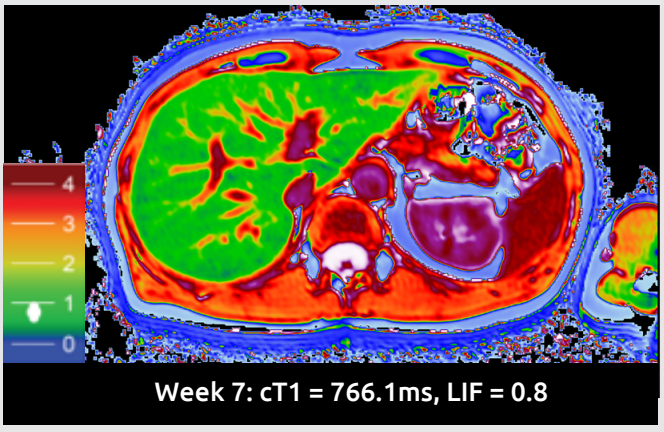
CASE STUDY 4 Hepatitis C

A 51 year old male, with Hepatitis C since 1984, received Interferon treatment in 2014 that was unsuccessful. However, Liver*MultiScan* Discover scans at Week 0 (left) and Week 7 (right) showed ledipasvir/sofosbuvir treatment - a reduction in LIF score corresponded to viral clearance.

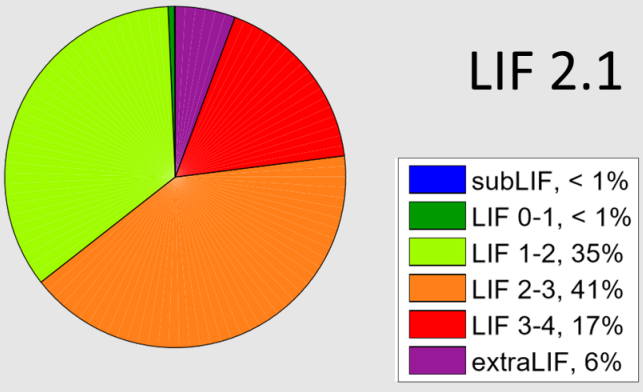
Enhanced analysis performed with Liver*MultiScan* Discover enables segmentation of and assessment across a whole liver slice, offering global statistics and insight into tissue heterogeneity. The pie charts show distribution of LIF scores within each respective slice, providing an objective and quantified method to monitor disease.



Week 0: cT1 = 881.8 ms, LIF = 2.1

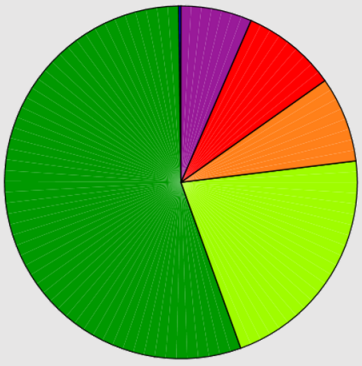


Week 7: cT1 = 766.1ms, LIF = 0.8



LIF 2.1

subLIF, < 1%
LIF 0-1, < 1%
LIF 1-2, 35%
LIF 2-3, 41%
LIF 3-4, 17%
extraLIF, 6%



LIF 0.8

subLIF, < 1%
LIF 0-1, 55%
LIF 1-2, 21%
LIF 2-3, 8%
LIF 3-4, 9%
extraLIF, 7%

CONCLUSIONS

The multiparametric MRI techniques in Liver*MultiScan* provide unparalleled liver image analysis services that support clinical trials in a variety of ways:

- Screening of patients with suspected NAFLD/NASH to establish the population prevalence of fatty liver disease and increase recruitment;
- Enriching clinical studies at enrollment, using predefined thresholds for cT1/LIF score to reduce wasted costs;
- Measuring changes in liver fat, iron and fibro-inflammatory disease, and distribution of the burden of disease, in the same patient over time, with accuracy and standardized metrics;
- Providing an endpoint for clinical studies to evaluate investigational therapies for the treatment of NAFLD/NASH

Such strategies can improve patient recruitment, stratification and the monitoring of short- and long-term outcomes of treatment interventions, enabling cost-savings to be realized through reduced timelines and earlier go/no-go decisions.

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