LiverMultiScan for liver disease

Medtech innovation briefing

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Summary

- The **technology** described in this briefing is LiverMultiScan, MRI-based imaging software. It is intended to be used for characterising liver tissue in people with suspected or confirmed liver disease. Using multiparametric MRI images, the software provides a quantitative assessment of liver fat, and quantitative biomarkers that correlate with liver iron concentration and fibro-inflammation.

- The **innovative aspect** is that it is a non-invasive procedure that does not need contrast agent. LiverMultiScan generates imaging markers for the estimation of extracellular fluid, liver iron and fat. It is claimed to improve the speed and reproducibility of liver tissue assessment. A single scan takes about 15 minutes.

- The intended **place in therapy** would be with MRI in secondary care for people with liver disease when a liver biopsy is being considered and their initial assessments are equivocal.

- The **main points from the evidence** summarised in this briefing are from 4 observational UK studies including 428 people with suspected or confirmed liver disease. The results of these studies suggest that MRI with LiverMultiScan provides good diagnostic accuracy for the assessment of liver fibrosis, inflammation, steatosis and haemosiderosis, and may predict clinical outcomes including liver-related events in people with liver disease.

- **Key uncertainties** around the evidence or technology are that the evidence is limited, and the diagnostic accuracy and cost effectiveness of LiverMultiScan compared with current invasive and non-invasive diagnostic techniques is uncertain.

- The **cost** of LiverMultiScan is £200 per scan for data analysis and reporting. The cost would be

- in addition to an MRI scan and standard care but the **resource impact** may be lower if the technology reduces the need for liver biopsy.

The technology

LiverMultiScan imaging software is used for characterising liver tissue. It is designed to be used with MRI to help clinicians to diagnose and stage liver disease. MRI is sensitive to subtle differences in tissue composition. It can scan the entire liver to provide measurements to help in the diagnosis and management of liver disease. No contrast agent is needed.

LiverMultiScan software uses patented technology to process MRI data for quantitative characterisation of the liver, providing standardised imaging markers as measures of liver tissue. The technology acquires measurements for the estimation of extracellular fluid (T1 map) and liver iron (T2* map). The presence of an increase in extracellular fluid is an indicator for inflammation and fibrosis in the liver. The presence of iron, that can be measured from T2*, can interfere with the assessment of extracellular fluid. An algorithm has been developed that allows for the bias introduced by elevated iron to be removed from the measurement of extracellular fluid, generating the iron-corrected T1 (cT1). LiverMultiScan also generates proton density fat fraction maps to quantify liver fat content.

LiverMultiScan is compatible with a range of MRI scanners and field strengths. The technology should not be used for pregnant women, people with a cardiac pacemaker, metal implants or fragments and tattoos (some tattoos are a contraindication for MRI if the ink used contains traces of metal).

Innovations

Unlike liver biopsy, LiverMultiScan is a non-invasive procedure. It produces maps showing the correlations of liver fibrosis or inflammation and the content of iron and fat. The company claims that a single scan with LiverMultiScan for liver tissue assessment takes about 15 minutes.

Current care pathway

Liver biopsy and transient elastography are the most common methods of assessing fibrosis in people with chronic hepatitis B and chronic hepatitis C in the NHS. The NICE Pathway on liver conditions includes interactive flowcharts for people with liver conditions. The positioning of LiverMultiScan in the pathway may differ depending on the referral pathway for specific liver conditions including alcohol-related liver disease, cirrhosis, hepatitis, liver cancer and non-alcoholic fatty liver disease when other tests (non-invasive or invasive) have been recommended.

NICE's guideline on hepatitis B (chronic) recommends transient elastography as the first test for liver disease in adults newly referred for assessment, and liver biopsy is offered or considered on the basis of a transient elastography score.

NICE's guideline on cirrhosis in over 16s recommends transient elastography for the diagnosis of cirrhosis and either transient elastography or acoustic radiation force impulse imaging (whichever is available) for the diagnosis of cirrhosis in people with non-alcoholic fatty liver disease and advanced liver fibrosis. Liver biopsy is considered for the diagnosis of cirrhosis in people for whom transient elastography is not available.

NICE's guideline on non-alcoholic fatty liver disease (NAFLD) recommends a liver ultrasound to test children and young people for non-alcoholic fatty liver, and to consider using the enhanced liver fibrosis test in people who have been diagnosed with non-alcoholic fatty liver disease to test for advanced liver fibrosis.

Population, setting and intended user

LiverMultiScan is intended to be used with MRI in a secondary care setting to help diagnose people with suspected or confirmed liver disease. The MRI based on the LiverMultiScan imaging protocol would most likely be done by radiologists in the radiology department. The scan is transferred through a secure portal (Edison) and is processed externally by the company (Perspectum Diagnostics) in the UK. Once the data have been analysed and reviewed, the report is returned within 48 hours to the clinicians (usually hepatologists). The company states that data processing is compliant with the Health Insurance Portability and Accountability Act, which sets the standard for sensitive patient data protection. Reports are checked by 2 independent assessors.

Costs

Technology costs

The company claims that LiverMultiScan is delivered based on a 'software as a service' model and does not need any additional hardware at the clinical site. The protocol for obtaining images for use with LiverMultiScan is based on standard, clinically available MRI sequences. The cost of LiverMultiScan is £200 per scan, which covers image processing and reporting.

Costs of standard care

The company states that the cost of a liver biopsy is between £497 and £553. The cost of an MRI scan of 1 area of the body without contrast, ranges between £116 and £133 depending on age. An

ultrasound scan costs between £40 and £49, and the cost of ultrasound elastography is £32 (NHS national tariff 2018/2019).

Resource consequences

LiverMultiScan is increasingly used in research. It has the potential to reduce the need for invasive liver biopsy.

A model based study (Blake et al. 2016) assessed the effect of non-invasive techniques in the diagnosis of non-alcoholic fatty liver disease in the diagnostic pathway. Three diagnostic pathways were compared in the study: LiverMultiScan, transient elastography, and transient elastography plus LiverMultiScan. A decision-tree model analysis suggested that the use of LiverMultiScan alone expected a 16% reduction in the number of biopsies needed, and there was an estimated reduction in the number of liver biopsies by 66% when LiverMultiScan was used with transient elastography.

A recent model analysis (Eddowes et al. 2018) evaluated the cost effectiveness of LiverMultiScan in the assessment of non-alcoholic fatty liver disease (n=56). The study reported LiverMultiScan could save an estimated £150,218 per 1,000 patients compared with biopsy. Combined transient elastography and LiverMultiScan provided additional savings over multiparameter MRI alone. The estimated cost per correct diagnosis was £554.26 using LiverMultiScan alone, which reduced to £307.92 using LiverMultiScan with transient elastography.

Regulatory information

LiverMultiScan is CE marked as a class IIa medical device. It is intended to be used with MRI to help clinicians assess liver tissue characteristics for the diagnosis of liver disease. No adverse events and medical device alerts for this technology have been identified.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

There are different types of liver diseases which can be associated with alcohol, obesity, viral infection, and genetic factors. Many liver diseases do not cause any symptoms in the early stages, and develop over the course of time, leading to be long-term conditions. This may mean someone is disabled if their liver disease has a substantial and long-term effect on their abilities to do daily activities. Disability is a protected characteristic under the Equality Act. LiverMultiScan is

contraindicated if MRI is not suitable for the individuals who are also protected under the Equality Act.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Four observational studies involving 428 people with liver disease are summarised in this briefing.

Table 1 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

Four studies are included in this briefing, but further evidence was identified as abstracts (n=30). Three observational studies included in table 1 evaluate the diagnostic accuracy of multiparametric MRI using LiverMultiScan to assess people with liver disease, compared with imaging markers such as fibrosis (extracellular water) and iron content with liver histology as the reference standard. Evidence suggested that multiparametric MRI provided good diagnostic accuracy for assessing liver fibrosis, inflammation, steatosis and haemosiderosis, and could potentially improve the assessment for people with liver disease such as non-alcoholic fatty liver disease and cirrhosis.

One study (Pavlides et al. 2016) examined the use of multiparametric MRI in patients with chronic liver disease. It suggested that the liver inflammation and fibrosis (LIF) score and a direct mapping of corrected T1 (cT1) calculated using LiverMultiScan predicted clinical outcomes including all-cause mortality and liver-related events such as liver-related death, the development of hepatocellular carcinoma and new episodes of hepatic decompensation.

Overall, results are likely to be generalisable to the NHS because all studies were done in the UK.

Table 1 Summary of selected studies

Banerjee et al. (2014)

Study size, design and location	A prospective, comparative study. UK.
Intervention and comparator(s)	MRI image with LiverMultiScan software. Liver biopsy.
Key outcomes	Paired MRI and biopsy data were studied in 79 patients with liver disease. MRI measures correlated strongly with histological results of liver biopsy. In all patients, MRI cT1 correlated with increasing liver fibrosis (r_s=0.68, p<0.0001). MRI measure of hepatic lipid content correlated with semi-quantitative steatosis scores (r_s=0.89, p<0.0001). Hepatic iron content showed a strong negative correlation with T2 map of liver by MRI, indicating the diagnosis of haemosiderosis (r_s=0.69, p<0.0001).
Strengths and limitations	A prospective study design. MRI operators were blinded to the indication for liver biopsy and to the patients' clinical details. The histopathologists were blinded to the MRI data. The author noted that liver biopsy is not an ideal reference standard for fibrosis, steatosis or haemosiderosis. Three study authors are on the board of directors and shareholders of the company.
Pavlides et al. (2016)	
Study size, design and location	A cohort study. UK.
Intervention and comparator(s)	MRI image with LiverMultiScan software. No comparator.

Key outcomes	The study included a total of 117 patients with liver disease and 112 with MRI data were included in the analysis. MRI maps were acquired for the estimation of extracellular fluid and liver iron content. Liver fat content was also estimated. LIF (a direct mapping of cT1) derived from MRI was used to categorised stages of liver disease, as follows: • LIF less than 1, no liver disease • LIF 1 to 1.199, mild liver disease • LIF 2 to 2.99, moderate liver disease • LIF 3 to 4, severe liver disease. When stratified using the LIF score, 22 patients (20%) had no liver disease, 34 (30%) had mild disease, 18 (16%) had moderate disease and 38 (34%) had severe disease. Patients were followed up after participating in the study (median=27 months), and all 22 patents with LIF less than 1 had no liver-related events found. There were 10 patients who developed liver-related events including 2 patients with moderate liver disease and 8 patients with severe liver disease. Kaplan-Meier analysis showed that patients with a LIF of 3 or more had a significantly higher cumulative risk of developing liver associated clinical complications including deaths over time compared with those with LIF less than 1 (p=0.02), and those with mild liver disease (LIF 1 to 1.99, p=0.03).
Strengths and limitations	The study included patients with liver disease, who were followed up to report any liver disease related outcomes. The length of follow-up was short to detect relevant events. Of the 9 study authors, 5 are shareholders of the company, and 2 are employees.
Pavlides et al. (2017)	
Study size, design and location	A prospective pilot study. UK.
Intervention and comparator(s)	MRI image with LiverMultiScan software. Liver biopsy.

Key outcomes	The study included 78 patients with suspected or confirmed non-alcoholic fatty liver disease, and data from 71 patients were included in the analysis.
	LIF derived from MRI was used to assess fibrosis. There was a significant association between histological fibrosis and LIF (r_s=0.51, p<0.0001). A LIF cut-off of 3.0 had a sensitivity 91% and specificity 73% for the diagnosis of cirrhosis.
	The LIF score was significantly associated with histological ballooning grade (r_s=0.59, p<0.0001) and overall disease activity (sum of ballooning and lobular inflammation grade) (r_s=0.58, p<0.0001). A LIF cut-off of 1.2 had a sensitivity of 91% and specificity of 53% for diagnosis of ballooning grade greater than 0, and a LIF cut-off of 1.6 had a sensitivity of 90% and specificity of 61% for the diagnosis of activity grade 2 or less.
Strengths and limitations	This is a prospective study. The study author noted that the use of histology as the reference standard is a limitation of the study because of sampling and observer-dependent variability of biopsy. Of the 11 study authors, 7 are shareholders of the company, including 2 who are employed by the company.

McDonald et al. (2018)

Study size, design and location	A prospective cohort study in 2 centres.
	UK.
Intervention and comparator(s)	MRI image with LiverMultiScan software.
	Liver biopsy.
Key outcomes	A total of 161 patients with suspected or confirmed liver disease participated in the study. All had MRI and 156 had biopsies. MRI assessment of hepatic fibrosis-inflammatory was positively associated with liver fibrosis by liver biopsy (p<0.001). There was a negative correlation between histological liver iron content and MRI T2* map of iron accumulation (r_s=−0.34, p<0.001, n=142), and a significant difference in T2* between patients with and without histological iron deposition (p<0.001). A T2* cut-off of 18 milliseconds had a sensitivity of 83% and specificity of 63% for distinguishing patients with stainable iron from those without.

Strengths and limitations	This is a prospective study.
	The study included 23% (n=34) patients who had liver transplant, and a subgroup analysis was conducted in the study. The use of histology as the reference standard is a limitation of the study because of sampling and observer-dependent variability of biopsy. Of the 11 study authors, 4 are employees of the company involved in the development of the technology.

Abbreviations: cT1, iron corrected T1; LIF, liver inflammation and fibrosis score; r_s, Spearman's rank correlation coefficient; T2, 'true' T2; T2*, 'observed' T2.

Recent and ongoing studies

- RADICAL1: non-invasive rapid assessment of NAFLD using magnetic resonance imaging with LiverMultiScan. ClinicalTrials.gov identifier: NCT03289897. Status: recruiting. Indication: non-alcoholic fatty liver disease. Intervention: LiverMultiScan.

- RADICAL2: non-invasive rapid assessment of patients with liver transplants using magnetic resonance imaging with LiverMultiScan. ClinicalTrials.gov identifier: NCT03165201. Status: recruiting. Indication: non-alcoholic fatty liver disease after liver transplant. Intervention: LiverMultiScan.

- HEPAT1CA: quantifying liver health in surgical candidates for liver malignancies. ClinicalTrials.gov identifier: NCT03213314. Status: recruiting. Indication: liver cancer. Intervention: LiverMultiScan.

- KIDS4LIFE: assessing kids for liver inflammation and fibrosis using non-invasive MRI. ClinicalTrials.gov identifier: NCT03198104. Status: recruiting. Indication: liver disease. Intervention: LiverMultiScan.

- The company states that LiverMultiScan is currently being used in 2 clinical studies to examine the efficacy and the effect of the technology on managing suspected or confirmed autoimmune hepatitis in comparison with standard care.

Specialist commentator comments

Comments on this technology were invited from clinical specialists working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All 3 specialists were familiar with or had used this technology before.

Level of innovation

One specialist said LiverMultiScan was innovative compared with the current care pathway. One specialist noted that other non-invasive measures of liver function such as blood tests and transient elastography were available in the NHS. These were commonly used for staging liver disease in the NHS but none of these measures had the ability to adequately distinguish different stages of liver disease (liver fibrosis) and to capture or track any change in liver tissue. This specialist thought that the technology provided similar modalities to other non-invasive tests, and that MRI-based measures including MRI elastography and MRI-derived proton density fat fraction are becoming available in some specialist centres. Another specialist suggested the novel aspect of LiverMultiScan was for the iron-corrected T1 (cT1) measurement, which was a patented correction technique that removed the biasing effect of iron from the T1 measurement.

Potential patient impact

One specialist thought that LiverMultiScan would provide comprehensive evaluation of liver health and may reduce the need for a liver biopsy when results of other conventional non-invasive tests were indeterminate. This specialist suggested that LiverMultiScan's quantification and assessment of fibro-inflammation could be useful in the stratification of patients with non-alcoholic fatty liver disease, especially in identifying high-risk non-alcoholic steatohepatitis patients who were at high risk of liver disease progression. Another specialist said that the technology would produce a liver heat map which provided the distribution of disease within the liver, which may have a positive effect on patients' management. One specialist did not think that there was any benefit to patients that was supported by the evidence.

Potential system impact

One specialist said LiverMultiScan may lead to reductions in the number of liver biopsies, but further evidence was needed to support its prognostic capability. This specialist also thought LiverMultiScan may need extra resources in radiology departments such as additional time for an MRI scan, initial set up and staff training. One specialist agreed that the technology could reduce the need for liver biopsies and may detect disease early to improvement the monitoring and management of patients. Another specialist did not think there would be any benefit to the health system; on the contrary, the use of the technology would add substantial demand on the system because of the potential increase in the number of patients having MRI scanning.

General comments

All specialists thought the technology was unlikely to replace current standard of care and felt the technology could be used as well as current tests. Specialists agreed that more high-quality evidence was needed to evaluate clinical effectiveness of LiverMultiScan.

Specialist commentators

The following clinicians contributed to this briefing:

- Philip Newsome, professor of hepatology, University of Birmingham, involving in research studies with the manufacturer of FibroScan, EchoSens.

- Jonathan Fallowfield, honorary consultant hepatologist, professor of translational liver research, University of Edinburgh, co-principal investigator and co-author on the Innovate UK funded study (McDonald et al. 2018) and co-investigator for an ongoing study (HepaT1ca, NCT03213314).

- Jeremy Cobbold, consultant hepatologist and clinical lead for hepatology, John Radcliffe Hospital, Oxford University Hospital NHS Foundation Trust, in collaboration with the company using LiverMultiScan in clinical research. Co-author on Pavlides et al. 2017.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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