



Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic exploration report number:	TER313
Topic:	LiverMultiScan for the diagnosis and staging of non-alcoholic fatty liver disease (NAFLD)
Summary of findings:	<p>LiverMultiScan is artificial intelligence-enabled quantitative imaging software that characterises the health of the liver using multiparametric magnetic resonance imaging (MRI). It does not require the use of contrast and is non-invasive.</p> <p>NICE guideline NG49 (2016) considered the assessment and management of NAFLD, but did not include the use of LiverMultiScan. In 2019, the NICE MedTech Innovation briefing on LiverMultiScan for liver disease concluded that evidence was limited, and the diagnostic accuracy and cost-effectiveness of LiverMultiScan compared with current invasive and non-invasive diagnostic techniques was reportedly uncertain.</p> <p>There is emerging evidence that LiverMultiScan could reduce the need for liver biopsy. However, there are significant uncertainties about the place of LiverMultiScan in the pathway and the cost-effectiveness of the technology. NICE currently have guidance in development (GID-DG10045) on LiverMultiScan MRI imaging software for the diagnosis and characterisation of NAFLD, which is expected to be published in October 2022.</p>

Introduction and aims

NAFLD is the most common form of metabolic liver disease, occurring in approximately 30% of all adults, and affects half of both people with obesity and people with type 2 diabetes. NAFLD is also the most common chronic liver disease in children and young people in industrialised countries, mainly because of obesity. In most people, NAFLD is asymptomatic and is only detected incidentally when blood tests or ultrasounds are performed for other reasons. Furthermore, 80% of people with NAFLD have normal routine liver blood tests and may remain undiagnosed. If NAFLD remains untreated, it can progress to more its more serious form of non-alcoholic steatohepatitis (NASH), where the liver is inflamed and becomes damaged. After NASH develops, there is an increased risk of serious health events that are associated with morbidity and mortality, including fibrosis, cirrhosis and hepatocellular cancer.

LiverMultiScan is artificial intelligence-enabled quantitative imaging software that characterises the health of the liver. It is used to analyse images that have been captured using multiparametric MRI. It is intended to aid the diagnosis, staging and monitoring of liver disease as part of the NAFLD diagnostic pathway, and is deployed globally through Software as a Service (SaaS). The LiverMultiScan procedure is non-invasive and does not require the use of contrast, and takes less than 15 minutes. However, its reliance on MRI-technology present issues for its use.

Health Technology Wales researchers searched for evidence on the clinical and cost-effectiveness of LiverMultiScan for the diagnosis and staging (as part of diagnostic pathway) of NAFLD.

Evidence overview

LiverMultiScan is a digital health technology and was determined to be a Tier C technology according to the [Evidence Standards Framework for Digital Health Technologies](#). This classification covers technologies with measurable user benefits, including tools used for treatment and diagnosis, as well as those influencing clinical management through active monitoring or calculation. For technologies of this classification, it is recommended that high quality RCTs with outcomes relevant to patients are produced to demonstrate effectiveness of the technology.

Technology assessments and guidelines

NICE guideline NG49 (2016) considered the assessment and management of NAFLD, but did not include the use of LiverMultiScan. The guideline recommends a liver ultrasound to test children and young people for NAFLD, and to consider using the enhanced liver fibrosis test in people who have been diagnosed with NAFLD to test for advanced liver fibrosis. However, it also notes that diagnostic practice varies and includes clinical, biochemical and radiographic tests. Due to evidence gaps, there were recommendations for research into non-invasive tests for diagnosing:

- NAFLD in adults
- NASH in people with NAFLD
- NAFLD and advanced liver fibrosis in children and young people.

The guideline stated that there is an urgent need for a simple, accessible, cost-effective, non-invasive test capable of case-finding NAFLD in the huge numbers of people at risk (noting type 2 diabetes and metabolic syndrome as risk factors). Diagnostic accuracy was considered high for MRI-based techniques, but they were described as impractical or too expensive for large-scale identification of cases. It was highlighted that MRI-based techniques are increasingly used as comparators in studies assessing non-invasive tests for NAFLD, because it is not feasible to carry out the diagnosis 'gold standard' of liver biopsies on a large scale. In addition, the guideline noted that

diagnostic practice varies and includes clinical, biochemical and radiographic tests. The evidence review showed that few diagnostic techniques have been assessed in children and young people.

In 2019, NICE published a MedTech innovation briefing (MIB181) on LiverMultiScan for liver disease, based on four observational UK studies including 428 people with suspected or confirmed liver disease. It was concluded 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. LiverMultiScan costs £200 per scan for data analysis and reporting, in addition to the cost of an MRI scan (£116-£133) and standard care. The resource impact may be lower if the technology reduces the need for liver biopsy (which costs approximately £500). However, evidence was limited, and the diagnostic accuracy and cost-effectiveness of LiverMultiScan compared with current invasive and non-invasive diagnostic techniques was reportedly uncertain.

NICE now have guidance in development (GID-DG10045) on LiverMultiScan MRI imaging software for the diagnosis and characterisation of NAFLD, which is expected to be published in October 2022. LiverMultiScan could reduce the need for liver biopsy. The topic description also highlights the claim that it will improve the speed, reliability and reproducibility of liver tissue assessment.

Systematic reviews and meta-analyses

Andersson et al. (2021) presented a pooled analysis and meta-analysis. Data was included from 5 clinical studies in which people with suspected NAFLD underwent multiparametric MRI with LiverMultiScan and a liver biopsy (n=485). Significant correlation was found with multiparametric MRI measures and histopathological markers from biopsy of NASH. The correlation with fibrosis was non-linear for liver fat by proton density fat fraction (PDFF), but linear and moderately strong for corrected T1 (cT1; $r_s = 0.51$). The ability of liver fat by PDFF and cT1 to identify at-risk NASH was 0.69 (0.64-0.74) and 0.79 (0.74-0.83) respectively in the pooled analysis. In the meta-analysis, the cluster-adjusted Area Under the Receiver Operating Characteristic curve (AUROC) was 0.66 (0.57-0.76) and 0.75 (0.70-0.80). Further improved diagnostic accuracy was observed with cT1 composite (cT1, AST and fasting glucose) scores in the validation dataset (AUROC: 0.84 [0.79-0.88]). This was confirmed in the cluster-adjusted meta-analysis (AUROC: 0.79 [0.70-0.87]).

Selvaraj et al. (2021) provided a large systematic review of imaging/elastography biomarkers in NAFLD. However, only two of the studies included used LiverMultiScan (to measure cT1). Diagnostic performance was assessed for distinguishing NASH from simple steatosis (area under curve [AUC] 0.69 and 0.80). Meta-analysis on MRI data was not completed due to the low number of primary studies. The authors noted, however, that cT1 had typically high sensitivity and low specificity.

Primary studies

A prospective observational study of people who underwent a liver biopsy for suspected NASH was presented by Imajo et al. (2021; n=145). People were screened using non-invasive techniques including multiparametric MRI to measure PDFF and cT1, as well as elastography techniques (vibration-controlled transient elastography [VCTE] liver stiffness measure, magnetic resonance elastography (MRE) and 2D Shear-Wave elastography [SWE] to measure stiffness and fat (controlled attenuated parameter, CAP). For identifying patients with NASH, PDFF and cT1 (both measured with LiverMultiScan) were the strongest performing individual measures (AUC: 0.80 and 0.75 respectively), and combined (PDFF plus cT1) were the overall best non-invasive test (AUC: 0.83). Although the additional benefit of combining measures was modest. The study concluded that quantitative multiparametric MRI is an effective alternative to liver biopsy for diagnosing NASH and NAFLD, and thus may offer clinical utility in patient management.

McDonald et al. (2018) reported on a prospective two-centre validation study (n=161). The authors concluded that LiverMultiScan demonstrated good diagnostic accuracy for detecting fibro-inflammatory injury, fat and iron in the liver across a range of disease severity and aetiology, and with excellent repeatability and reproducibility. Diagnostic performance was comparable to existing well-validated non-invasive biomarkers. A subgroup analysis in people with NAFLD was reported separately by Eddowes et al. (2018; see economic evaluations below). Another validation study by Bachtiar et al. (2019) showed that cT1, T2 and PDFF (using LiverMultiScan) had high repeatability and reproducibility across different manufacturers, field strength, and scanner model combinations on 61 participants who had mixed liver disease aetiology as well as those without any history of liver disease.

A qualitative study of 101 participants diagnosed with a range of liver disease aetiologies was reported by McKay and Pantoja (2020). People demonstrated a clear and strong preference for non-invasive tests over biopsy. The authors concluded that the LiverMultiScan visual report was an effective contributor to better patient experience and increased understanding of liver disease. This was considered particularly important for people with NAFLD because they seemed to have less understanding of their condition and are reportedly likely to have fewer patient-focused support groups in comparison to other chronic liver disease conditions.

Economic evaluations

Eddowes et al. (2018) evaluated the cost-effectiveness of LiverMultiScan for the assessment of NAFLD (n=56). The authors reported that LiverMultiScan could save an estimated £150,218 per 1,000 people compared with biopsy. Additional savings were observed when LiverMultiScan was combined with transient elastography (compared to multiparametric MRI alone). The estimated cost per correct diagnosis was £554.26 using LiverMultiScan alone, which reduced to £307.92 using LiverMultiScan with transient elastography.

Blake et al. (2016) used a simple decision-tree model to compare the costs associated with diagnostic pathways for NAFLD that use non-invasive techniques. The use of multiparametric MRI as an adjunct to transient elastography, while increasing screening costs, was predicted to reduce the number of liver biopsies by 66%. Used as the sole diagnostic scan, there remains an expected 16% reduction in the number of biopsies required.

Areas of uncertainty

NICE NG49 and MIB181 provide some evidence and recommendations, but there remain significant uncertainties around the place of LiverMultiScan in the pathway and practicality of delivery and there are remaining uncertainties around diagnostic accuracy and cost-effectiveness.

NICE currently have guidance in development (GID-DG10045) on LiverMultiScan MRI imaging software for the diagnosis and characterisation of NAFLD. This guidance is expected to address these areas of uncertainty in detail.

Literature search results

Health Technology Assessments and Guidance

NICE. (expected 2022). LiverMultiScan MRI imaging software for the diagnosis and characterisation of non-alcoholic fatty liver disease (provisional title). NICE guidance in development GID-DG10045. Available at: <https://www.nice.org.uk/guidance/indevelopment/gid-dg10045> [Accessed 25 Aug 2021].

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SHTG. (2018). Direct tests for liver disease. SHTG Advice Statement 010-18. Scottish Health Technologies Group. Available at: <https://shtg.scot/our-advice/direct-tests-for-liver-disease> [Accessed 25 Aug 21].

SHTG considered tests for detecting and staging liver fibrosis and cirrhosis in patients with diagnosed or suspected NAFLD, alcohol-related liver disease, or viral hepatitis. No relevant information on diagnosis of NAFLD or NASH was provided.

Evidence reviews and economic evaluations

Blake L, Duarte RV and Cummins C. (2016) Decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multiparametric magnetic resonance imaging. *BMJ Open*. 6(9):e010507. doi: <http://dx.doi.org/10.1136/bmjopen-2015-010507>

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Selvaraj EA, Mózes FE, Ajmer Jayaswal AN, et al. (2021). Diagnostic accuracy of elastography and magnetic resonance imaging in patients with NAFLD: a systematic review and meta-analysis. *Journal of hepatology*. Vol unspecified: 1-16. doi: <http://dx.doi.org/10.1016/j.jhep.2021.04.044>

Individual studies

Harrison SA, Gawrieh S, Roberts K et al. (2021). Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. *Journal of Hepatology*. 75(2):284-291. doi: <https://doi.org/10.1016/j.jhep.2021.02.034>.

McDonald N, Eddowes PJ, Hodson J, et al. (2018). Multiparametric magnetic resonance imaging for quantitation of liver disease: a two-centre cross-sectional observational study. *Scientific Reports*. 8(1):9189. doi: <https://doi.org/10.1038/s41598-018-27560-5>.

Ongoing research

Tonev D, Shumbayawonda E, Tetlow LA et al. (2020). The Effect of Multi-Parametric Magnetic Resonance Imaging in Standard of Care for Nonalcoholic Fatty Liver Disease: Protocol for a Randomized Control Trial. *JMIR Research Protocols*. 9(10):e19189

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Pavlidis M, Levick C, Mozes F, et al. (2018). Diagnostic accuracy of imaging modalities for the staging of fibrosis and diagnosis steatohepatitis in patients with non-alcoholic fatty liver disease: protocol for a systematic review and meta-analysis. PROSPERO 2018 CRD42018116522 Available at: https://www.crd.york.ac.uk/prospéro/display_record.php?ID=CRD42018116522 [Accessed 31 August 2021]

Provided by the Topic Proposer through HealthTech Connect

Andersson A, Kelly M, Imajo K, et al. (2021). Clinical Utility of MRI Biomarkers for Identifying NASH Patients at High Risk of Progression: A Multicenter Pooled Data and Meta-Analysis. *Clinical Gastroenterology and Hepatology*.

Bachtiar V, Kelly M, Wilman HR, et al. (2019). Repeatability and reproducibility of multiparametric magnetic resonance imaging of the liver. *PLOS ONE*. 14(4): e0214921. <https://doi.org/10.1371/journal.pone.0214921>

Imajo K, Tetlow L, Dennis A, et al. (2021). Quantitative multiparametric magnetic resonance imaging can aid non-alcoholic steatohepatitis diagnosis in a Japanese cohort. *World Journal of Gastroenterology*. 27(7):609-623. doi: [doi.10.3748/wjg.v27.i7.609](https://doi.org/10.3748/wjg.v27.i7.609)

Jayaswal ANA, Levick C, Selvaraj EA, et al. (2020). Prognostic value of multiparametric magnetic resonance imaging, transient elastography and blood-based fibrosis markers in patients with chronic liver disease. *Liver International*. 40(12):3071-3082. doi: <https://doi.org/10.1111/liv.14625>

McKay and Pantoja (date unknown; unpublished). Patient Understanding and Experience of Non-invasive Liver Diagnostic Techniques and the Liver Patient Pathway: A Qualitative Study. Unpublished report.

Date of search:	August 2021
Concepts used:	Biomarker; diagnos*; liver biopsy; LiverMultiScan; magnetic resonance imaging (MRI); non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); stag*; ultrasound