NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Final scope

September 2021

1 Introduction

The topic selection oversight panel identified LiverMultiScan software as potentially suitable for evaluation by the diagnostics assessment programme based on a MedTech Innovation Briefing and further information provided by the manufacturer.

The final scope was informed by discussions at the scoping workshop on 1st September 2021 and at the assessment subgroup meeting on 15th September 2021.

A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the technologies based on information provided by manufacturers and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technologies

Following diagnosis of non-alcoholic fatty liver disease (NAFLD), further assessment of the liver is done to help inform clinical management of the condition. Currently used tests assess levels of liver fibrosis and include blood-based biomarkers, acoustic radiation force impulse imaging (ARFI), transient elastography and liver biopsy.

MRI could be an option for non-invasive assessment of liver disease, either through elastography or multiparametric MRI (Schaapman et al. 2021), to further evaluate the level of fibrosis or fibro-inflammation. Results from MRI assessment could help make decisions about whether a liver biopsy is needed and about the extent of future monitoring. They may also allow

targeted offering of lifestyle interventions or improve uptake and compliance with these interventions to reduce the likelihood of progression to more severe NAFLD. Clinical experts have advised that the ability of MRI to image the whole liver could also aid in targeting biopsies to sample particular areas of interest.

2.2 Product properties

2.2.1 LiverMultiScan

LiverMultiScan is a standalone software application produced by Perspectum Ltd. that provides quantitative multiparametric analysis of non-contrast magnetic resonance images. LiverMultiScan is intended to aid clinicians in the diagnosis and staging of NAFLD. No additional hardware is required, and the sequences required to obtain the images can be integrated into existing abdominal MRI scans on Siemens, Philips, or GE Healthcare scanners. LiverMultiScan uses iron-corrected T1 (cT1), proton density fat fraction (PDFF) and T2* MRI protocols for its analyses. The total time for the scan is typically 15 minutes.

cT1 outputs are measured in milliseconds (ms), and correlate with liver fibro-inflammation. The company claim that cT1 also correlates with biopsy scores as described in section 3.2.2.2. Values have been proposed by the company for the staging of fibro-inflammation, associated diagnoses, and clinical management options:

- **Less than 800 ms:** “Fatty liver”
  - Reassure as no inflammation present
  - Reassess with MRI in 3 years
- **800 to 875 ms:** “Non-alcoholic steatohepatitis (NASH)”
  - Lifestyle modification
  - Management of type 2 diabetes and cardiovascular disease
  - Monitor disease status with MRI after 6 months
- **More than 875 ms:** “High-risk NASH”
  - Reassess with MRI every 6 months
  - Consider liver biopsy if cirrhosis is suspected
  - Cancer surveillance
  - Consider inclusion in NASH therapeutic trials

MRI PDFF is an MRI measurement of fat content and is expressed as a percentage. The company states that a normal reference range for PDFF is less than 5.6%.

Acquired imaging data is transferred to a portal operated by Perspectum, where it is analysed by their UK-based team of clinical image analysts to form a report containing quantitative liver tissue characteristics across the whole liver (cT1, PDFF and T2* results, acquisition details, and optional segmentation analyses). The company state that the cloud-based reports are available to the requesting clinician within 48 hours of the MRI.

The company state that setup of the LiverMultiScan protocol can be completed by an MR operator, following instructions from Perspectum Ltd. Training on how to use the protocol takes approximately 3 hours. Specialist technical support is provided by the manufacturer as part of the licence.

2.2.2 Resoundant magnetic resonance elastography (MRE) system

MRE combines MRI with low-frequency vibrations to create a 2D or 3D elastogram showing the stiffness of tissue. In addition to the MRI equipment required, vibrations are created using an external mechanical driver that passes vibrations through a flexible tube to a passive driver placed on a person's abdomen over the liver. The driver is manufactured by Resoundant, Inc. and is compatible with MR scanners from Siemens, Philips, or GE Healthcare. Access to MRE hardware and software is requested via and installed by the scanner manufacturer.

MRE is used for detecting and evaluating different stages of fibrosis. The MRE acquisition is performed during breath-holding and takes 12 to 15 seconds, which is typically repeated 4 times. The total acquisition time is less than 1 minute. MRE is usually added to a conventional abdominal MRI protocol.

MRE outputs are provided in kilopascals (kPa). The manufacturer has suggested the following thresholds for staging liver fibrosis (see section 3.2.2.2 for more detail):

- **Any fibrosis:** 2.9 kPa
- **Significant fibrosis:** 3.3 kPa
- **Advanced fibrosis:** 3.9 kPa
- **Cirrhosis:** 4.8 kPa

MRE can be used alongside standardised MRI fat-fraction and iron-assessment packages offered by scanner manufacturers to provide an overview of liver fibrosis, fat, and iron. The company states that the scanner time required for these protocols would be less than 10 minutes.

3 Target conditions

3.1 NAFLD and NASH

NAFLD is the term for a range of conditions caused by a build-up of fat in the liver (NHS 2018). It is estimated that between one in three (NHS 2018) and one in five (British Liver Trust 2018) people in the UK are in the early stages of the condition. It mainly affects people aged 50 or over and is more common in men than women. Other risk factors include type 2 diabetes, high blood pressure, higher cholesterol, metabolic syndrome, and smoking. Certain drugs and genetic conditions are also associated with fatty liver disease. Although less common in children and young people, obesity rates are rising in this demographic (National Child Measurement Programme 2020/21), and NAFLD may be present in 38% of obese children (Mann et al. 2015).

While most people with mild NAFLD do not experience any symptoms, they may experience tiredness or discomfort on the right side of their body. Those with more advanced disease may experience weakness, jaundice, swelling, itchy skin and eventually liver failure or liver cancer. NAFLD develops in 4 stages:

- Simple fatty liver (steatosis): a largely harmless build-up of fat in the liver cells.
- NASH: build-up of fat leads to inflammation. It is estimated that up to 5% of the UK population are affected by NASH (NHS 2018).
- Fibrosis: persistent inflammation causes scar tissue to develop in the liver and nearby blood vessels, but the liver still functions normally (NHS 2018). It is estimated that 10 to 15% of people with NAFLD will develop fibrosis (Public Health England 2020).
- Cirrhosis: severe scarring from chronic inflammation, causing permanent damage. Around 1 in 5 people with NASH progress to cirrhosis (British Society of Gastroenterology [BSG] guidance on NAFLD – diagnosis, assessment and management, 2020).

NASH is diagnosed histologically by the presence of inflammation and ballooning hepatocytes (Brunt et al. 2015). The NAFLD Clinical Research Network (CRN) system uses the NAFLD activity score (NAS), which combines scores for steatosis, inflammation and ballooning, but does not include fibrosis (Kleiner et al. 2005). Most people with a NAS of 5 or greater are diagnosed with NASH.

People with liver fibrosis are at increased risk of death, with stage of fibrosis being the most influential predictor of all-cause or liver-related mortality (Dulai

et al. 2017). People with NASH may progress faster to fibrosis than those with simple fatty liver (Singh et al. 2015).

Cirrhosis and other liver diseases are the leading cause of death in the UK in people aged 35 to 49 years (Public Health England 2020). Most of this liver disease is alcohol related. However, NAFLD prevalence is increasing alongside overall levels of obesity in the population. Clinical experts have described NAFLD as an oncoming epidemic. The Lancet commission into liver disease in the UK recommended that early identification and management of liver disease is an essential prerequisite to improve outcomes and avoid complications in NAFLD (Williams et al. 2021).

Treatment for NAFLD with no or minimal fibrosis consists of education on risk factors for advanced fibrosis, and advice on weight management. Those with advanced liver fibrosis may be offered pioglitazone or vitamin E (NICE guidance NG49), although clinical experts have advised that this may not be done in practice. People with advanced fibrosis may enter clinical trials or be considered for bariatric surgery for weight management.

3.2 Diagnostic and care pathway

3.2.1 Risk groups for NAFLD

NICE's guideline on the assessment and management of non-alcoholic fatty liver disease highlights that NAFLD is more common in people who have type 2 diabetes or metabolic syndrome. It also recommends taking an alcohol history to rule out alcohol-related liver disease, and not to use routine liver blood tests to rule out NAFLD.

Other risk factors that may prompt an investigation for fatty liver disease include (British Liver Trust 2018):

- being overweight or obese
- insulin resistance
- hypertension
- high liver enzyme, blood cholesterol, glucose, or triglyceride levels
- polycystic ovary syndrome
- smoking
- poor diet/low exercise.

Clinical experts have advised that NAFLD rarely occurs in isolation. People with NAFLD will often have a high level of alcohol intake or a comorbidity such as type 2 diabetes which can complicate the management or identification of the condition.

3.2.2 Diagnosis and referral

3.2.2.1 Diagnosis of NAFLD

If NAFLD is suspected based on risk factors, initial investigations should first exclude alternative causes through assessment of alcohol intake, history of steatosis-associated drugs, liver ultrasound, and bloodwork including tests for hepatitis B or C, and liver enzyme and insulin levels (BSG guidance on NAFLD – diagnosis, assessment and management, 2020, Byrne et al. 2018).

NICE's guideline on the assessment and management of non-alcoholic fatty liver disease includes recommendations for research for non-invasive tests for diagnosing NAFLD in adults.

The Royal College of General Practitioners (RCGP) suggest investigating potential NAFLD using liver ultrasound or the fatty liver index test (a composite measure of body mass index [BMI], waist circumference, gamma glutamyl transpeptidase [GGT] and triglyceride levels). GPs are warned that routine liver blood tests commonly return normal results in NAFLD, even when there is advanced liver fibrosis. A normal liver function test has no value in excluding a diagnosis of NAFLD or NASH.

Guidelines from the BSG Clinical Services and Standards Committee (Newsome et al. 2018) state that NAFLD is diagnosed by the presence of an echobright liver on ultrasound showing fat accumulation in the absence of excessive alcohol consumption.

To diagnose NAFLD in children and young people (up to 17 years old), NICE's guideline on the assessment and management of non-alcoholic fatty liver disease recommends to:

- Offer a liver ultrasound to test children and young people for NAFLD if they:
  - have type 2 diabetes or metabolic syndrome and
  - do not misuse alcohol.
- Refer children with suspected NAFLD to a relevant paediatric specialist in hepatology in tertiary care.
- Diagnose children and young people with NAFLD if:
  - ultrasound shows they have fatty liver and
  - other suspected causes of fatty liver have been ruled out.
- Offer liver ultrasound to retest children and young people for NAFLD every 3 years if they:
  - have a normal ultrasound and
  - have type 2 diabetes or metabolic syndrome and
  - do not misuse alcohol.

3.2.2.2 Staging of fibrosis

Once a diagnosis of NAFLD has been given, patients are assessed for liver fibrosis.

BSG recommendations (October 2020) suggest initial testing with the fibrosis-4 index for liver fibrosis (FIB-4) or the NAFLD fibrosis score (NFS).

The FIB-4 and NFS tests are blood-based diagnostic tests that can be carried out in primary care. The FIB-4 score is determined using patient age, platelet count, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The NFS score is determined using patient age, BMI and presence of impaired fasting glucose or diabetes, in addition to AST, ALT, platelet count and albumin levels.

To identify people with advanced liver fibrosis following a diagnosis of NAFLD, NICE's guideline on the assessment and management of non-alcoholic fatty liver disease recommends to:

- Offer testing for advanced liver fibrosis to people with NAFLD.
- Consider using the enhanced liver fibrosis (ELF) test in people who have been diagnosed with NAFLD to test for advanced liver fibrosis, and diagnose if they have an ELF score of 10.51 or above.
- Do not use routine liver blood tests to assess for advanced liver fibrosis in people with NAFLD.
- Refer adults and young people diagnosed with advanced liver fibrosis to a relevant specialist in hepatology.

Guidance recommends that people with blood-based biomarker scores indicating low risk of advanced fibrosis should return to primary care for monitoring every 2 to 3 years (BSG guidance on NAFLD – diagnosis, assessment and management, 2020, Byrne et al. 2018, EASL 2021). Those with scores indicating a high risk of advanced fibrosis should be referred to a hepatology clinic and may have liver biopsy. However, if blood-based tests are indeterminate, then the patient may have further tests such as the ELF test (if not done initially), or measurement of liver stiffness (for example, with transient elastography or ARFI). Clinical experts reported that in some centres, people with risk factors for NAFLD may be referred for transient elastography without any prior testing for fibrosis.

The Lancet commission into liver disease into the UK (Williams et al. 2021) suggests a similar clinical pathway to that recommended by the BSG.

European guidelines recommend that patented serum tests (for example, the ELF test) are used to confirm a high or intermediate outcome from transient

elastography. If the results are discordant with transient elastography, or the patented serum tests are unavailable, then liver biopsy should be considered to make a final diagnosis (EASL 2021).

Clinical experts advised that liver biopsy is done in a large proportion of patients in the NHS with significant or advanced fibrosis to either confirm diagnosis or in order to enter clinical trials. Biopsy may also be done to identify non-NAFLD liver conditions such as autoimmune hepatitis.

Fibrosis is histologically staged according to the NAFLD CRN system (Kleiner et al. 2005):

- F0: no fibrosis
- F1 (any fibrosis): perisinusoidal or periportal fibrosis
- F2 (significant fibrosis): perisinusoidal and portal/periportal fibrosis
- F3 (advanced fibrosis): bridging fibrosis (across lobules, between portal areas, or between portal areas and central veins)
- F4: cirrhosis.

NICE's guideline on the assessment and management of non-alcoholic fatty liver disease includes a recommendation for research for non-invasive tests for diagnosing NAFLD and advanced liver fibrosis in children and young people.

A 2020 survey of liver disease management by clinical commissioning groups (CCGs) and health authorities in the UK found that there was significant variation between centres for assessment of liver disease (Jarvis et al. 2021). Only 40% of CCGs had a pathway for assessing abnormal liver function tests, and 29% had a pathway for assessing liver disease more generally.

Indirect serum markers of fibrosis (for example FIB-4 and NFS) were used by 44% of responding organisations, compared with 16% using the ELF test and 25% using transient elastography. There were also differences between countries in the UK, with the ELF test and transient elastography being much more prevalent in Scotland and Wales than in England. Clinical experts and professional society representatives have commented that the ELF test is not widely available in the NHS (RCGP 2016).

Figure 1 presents a general overview of current testing for fibrosis done in people with NAFLD, based on clinical guidelines and clinical expert advice. As noted above, recommendations and practice across the NHS vary. For example, transient elastography or ARFI may be done after FIB-4 or NFS tests if they indicate a high risk of advanced fibrosis. Clinical experts highlighted that multiple tests could be done at each stage in some parts of the NHS. For example, both transient elastography and ELF may be used to

assess a patient with indeterminate FIB-4 results. This can create scenarios where there are discordant results between tests and uncertainty about subsequent care.

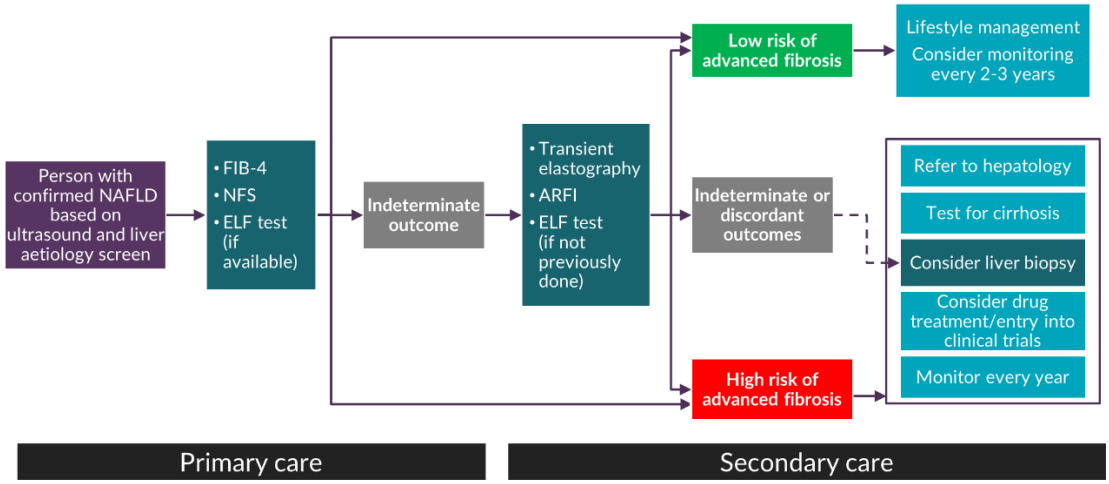

Figure 1: Overview of current pathway for assessment of fibrosis in the NHS, based on guidelines and expert advice.

3.2.2.3 Diagnosis of NASH

The diagnosis of NASH may be clinically relevant because NASH is associated with faster progression of liver fibrosis (EASL 2021). However, some guidelines state that it is clinically more important to stage fibrosis than to establish the presence of NASH (Byrne et al. 2018).

Although there are several non-invasive tests that are proposed to diagnose NASH, conflicting literature and lack of validation studies has led European guidance to state that liver biopsy remains the reference standard for the diagnosis of NASH in people with NAFLD (EASL 2021).

There are currently no NICE recommendations for the diagnosis of NASH. NICE's guideline on the assessment and management of non-alcoholic fatty liver disease includes a recommendation for research for non-invasive tests for diagnosing NASH.

3.2.2.4 Treatment

NICE's guideline on the assessment and management of non-alcoholic fatty liver disease has the following recommendations on lifestyle modification options for people diagnosed with NAFLD:

- Offer advice on physical activity and diet to people with NAFLD who are overweight or obese in line with NICE's obesity and preventing excess weight gain guidelines.

- Explain to people with NAFLD that there is some evidence that exercise reduces liver fat content.
- Consider the lifestyle interventions in NICE's obesity guideline for people with NAFLD regardless of their BMI.
- Do not offer omega-3 fatty acids to adults with NAFLD because there is not enough evidence to recommend their use.
- Explain to people with NAFLD who drink alcohol the importance of staying within the national recommended limits for alcohol consumption.

Clinical experts reported that the amount of weight loss recommended to a person with NAFLD would be proportional to their stage of liver fibrosis. For example, a person with F2 fibrosis may be recommended to lose 5% body mass, whereas a person with F3 may be advised to lose 10% instead.

Pharmacological treatment is recommended for consideration in people with NAFLD and advanced liver fibrosis only:

- In secondary or tertiary care settings only, consider pioglitazone or vitamin E for adults with advanced liver fibrosis, whether they have diabetes or not.
- In tertiary care settings only, consider vitamin E for children with advanced liver fibrosis, whether they have diabetes or not.
- In secondary or tertiary care settings only, consider vitamin E for young people with advanced liver fibrosis, whether they have diabetes or not.
- Offer to retest people with advanced liver fibrosis 2 years after they start a new pharmacological therapy to assess whether treatment is effective.
- Consider using the ELF test to assess whether pharmacological therapy is effective.
- If an adult's ELF test score has risen, stop either vitamin E or pioglitazone and consider switching to the other pharmacological therapy.
- If a child or young person's ELF test score has risen, stop vitamin E.

Clinical experts have advised that pioglitazone or vitamin E may not be prescribed in practice. There are currently no pharmacological treatments approved specifically for the treatment of NAFLD or NASH, although novel therapeutics are under clinical development (Piazzola & Mangia, 2020). People with significant fibrosis may be considered for entry into clinical trials for upcoming therapies.

In selected, severely obese cases, bariatric procedures may be considered (BSG guidance on NAFLD – diagnosis, assessment and management, 2020).

3.2.2.5 Further monitoring of liver disease for people with NAFLD

People with NAFLD who do not have advanced fibrosis are recommended to be monitored every 2 to 3 years (BSG guidance on NAFLD – diagnosis, assessment and management, 2020, Byrne et al. 2018, EASL 2021, NICE guideline on the assessment and management of non-alcoholic fatty liver disease). EASL guidance includes a weak recommendation to use non-invasive tests such as the FIB-4 or transient elastography for this purpose, and to monitor every year in people with advanced fibrosis (EASL 2021). Clinical experts confirmed that these tests would be used for monitoring purposes in the NHS.

Clinical experts highlighted that the frequency of monitoring done based on a person's level of fibrosis levels can vary in the NHS. In their experience, people with advanced fibrosis but no cirrhosis would be monitored every 6 months to 1 year, depending on clinical factors such as age and comorbidities. People with significant fibrosis may be monitored more frequently than is recommended in published guidance, for example every year.

People with advanced fibrosis are tested for cirrhosis. The NICE guideline for the assessment and management of cirrhosis in over 16s recommends to:

- Offer either transient elastography or ARFI (whichever is available) to diagnose cirrhosis for people with NAFLD and advanced liver fibrosis (as diagnosed by a score of 10.51 or above using the ELF test).
- Consider liver biopsy to diagnose cirrhosis in people for whom transient elastography is not suitable (for example people with obesity or who have not abstained from alcohol for the required period).

Guidance from the RCGP indicates that patients in which transient elastography or ARFI results do not diagnose cirrhosis would be offered lifestyle interventions to help prevent cirrhosis and retested for cirrhosis every 2 years.

Those with a result indicating cirrhosis from transient elastography, ARFI or biopsy would be monitored for end-stage liver disease and liver cancer every 6 months, tested for varices, offered treatment for complications of cirrhosis (for example variceal band ligation), and potentially offered prophylactic

treatment depending on co-morbidities (NICE guideline for the assessment and management of cirrhosis in over 16s, RCGP 2017).

3.2.2.6 Liver biopsy

The BSG state that biopsy is usually reserved for certain patients at high risk of advanced liver disease or with suspected concomitant secondary liver disease such as autoimmune hepatitis (BSG 2020). However, clinical experts have indicated that biopsy is regularly used to diagnose advanced fibrosis in some centres.

Experts commented that biopsy is most useful for cases of cirrhosis and differential diagnosis where other tests have failed, and that repeat biopsies (such as for monitoring) are not desirable. However, due to clinical trial entry requirements, patients with intermediate or advanced fibrosis may have liver biopsy for this purpose only.

Paediatric experts advised that biopsies are typically only done in children or young people where there is a need for further diagnostic investigation, such as rapid progression of disease with no apparent cause.

Complications caused by biopsy include bleeding (in some cases major bleeding), embolism and pain (Neuberger 2020). The incidence of complications is higher in people who are overweight or obese, which is of particular concern as these conditions affect most people with NAFLD.

The BSG recommends a single pass for biopsy to reduce the risk of complications (Neuberger et al. 2020). As only a small portion of the liver is analysed, there are issues of variability and sampling error. Furthermore, inter-observer variation in the interpretation of the biopsy outcomes can lead to unclear outcomes and the need for additional biopsy (Standish et al. 2006). Clinical experts commented that although liver biopsy is considered the gold standard to assess fibrosis and/or the presence of NASH, it is unlikely to be completely accurate (Standish et al. 2006).

3.3 Patient issues and preferences

Advanced liver disease can cause morbidity leading to time off work and potential early retirement. Therefore, earlier detection and treatment of liver disease may have financial and social benefits for people with NAFLD.

Liver biopsy is unpopular with patients as the procedure can be painful and can cause complications (see section 3.2.2.6). Patient representatives and clinical experts commented that biopsies represent a significant time commitment for patients and the clinic due to travel, pre-biopsy checks, time

for the actual procedure, and post-procedural monitoring. People may also have to spend some time off work during the recovery period. Liver biopsies can have social implications for children and young people due to need to travel, take time off school, and not to take part in physical activities during the recovery period. A clinical expert commented that avoiding biopsy may have particular benefit for people with psychiatric issues who may find biopsies particularly distressing.

MRI produces a visual map of the liver which may give people with NAFLD a greater understanding of their liver health and risk of adverse clinical outcomes. This may improve motivation to adhere to lifestyle interventions. Clinical experts have also commented that liver biopsy results can also act as a motivating factor for weight loss.

MRI procedures are generally tolerable to patients but may be uncomfortable or unusable for larger people due to the size of the scanner bore and bed. MRI techniques may also be unsuitable for people with claustrophobia.

There may be a need to travel potentially long distances to have imaging-based tests, such as MRI, if not available locally (see section 9).

The NHS website states that MRI techniques may not be suitable for people with ferrous metal implants or fragments in their body, extensive tattoos, or people who are pregnant (NHS, 2018). Clinical experts commented that MRI may be possible for people in these groups.

4 Position of MRI-based technologies in the care pathway for assessment

This section describes the populations for whom the use of MRI-based technologies will be assessed for in this guidance. Further detail on the described comparators is presented in section 5. Care pathway descriptions are based on current guidance and clinical expert advice (see section 3).

Clinical experts advised that using an MRI-based test as an initial assessment for liver health (that is, before or as an alternative to currently used tests) may not be feasible in the NHS because of available MRI capacity.

4.1 People with NAFLD for whom advanced fibrosis or cirrhosis has not been diagnosed

There may be limited utility for use of MRI-based tests for people that currently available tests (prior to any biopsy being done) have identified as having advanced fibrosis (F3) or cirrhosis (F4), in terms of what changes to care the tests would cause. Clinical experts also commented that for people

that currently available testing identifies as having low risk of advanced fibrosis, the scope for the tests to change care may also be limited.

In people for whom current tests for fibrosis identify as having an indeterminate result, for whom current tests cannot be used or have failed, or who have discordant results from previous tests (these groups are discussed further below), MRI-based tests may provide additional information about fibrosis levels or fibro-inflammation. This may impact on:

- decisions about the need for a biopsy
- targeting of biopsy location if it is decided a biopsy is necessary
- offering of targeted lifestyle interventions
- adherence to lifestyle advice
- the extent of monitoring offered.

For biopsy, clinical experts commented that based on LiverMultiScan results, biopsy would likely not be done if the result was less than 800 ms (that is, no fibro-inflammation). They would likely do a biopsy if the test result was higher than 800 ms. The company's suggested approach was to consider biopsy for people with a result of over 875 ms (see section 2.2.1).

With MRE, clinical experts advised that a result showing fibrosis of F2 or lower would likely mean that a biopsy would not subsequently be done.

Because fibro-inflammation, as measured by the LiverMultiScan, is not currently routinely measured in the NHS, there is uncertainty about the impact of this result on decisions about how often to monitor the liver for people with NAFLD and on what lifestyle interventions to offer. Monitoring of the liver for people with NAFLD is variable across the NHS and depends on available information on stage of fibrosis (see section 3.2.2.5). For some patients, monitoring could already be reasonably frequent. People with NAFLD often have diabetes or are obese and may already have access to all available lifestyle interventions provided by the NHS. The impact of MRI results on clinical decision making has been included as a relevant outcome for consideration in this assessment (see table 1).

4.1.1 People with indeterminate results from fibrosis testing

People with NAFLD who have transient elastography, ARFI, or the ELF test to assess the degree of fibrosis may get a result that indicates some level of fibrosis but is indeterminate with regards to whether advanced fibrosis (F3) is present.

Based on BSG guidance on NAFLD, an indeterminate score for transient elastography is between 7.9 and 9.6 kPa. EASL guidance states that scores less than 8 kPa are sufficient to rule out advanced fibrosis, but higher scores require further investigation either with patented blood tests such as ELF, and biopsy if this is not possible or in the case of discordant results (EASL 2021). An upper limit of 12 to 15 kPa is suggested as possible to rule in advanced fibrosis. McDonald et al. 2018 defined borderline transient elastography results as between 7 and 13 kPa.

NICE guidance on the management of chronic hepatitis B states that the degree of fibrosis cannot be accurately predicted in adults with a transient elastography score between 6 to 10 kPa, and that some people may choose to have a liver biopsy in these circumstances to confirm the extent of liver disease.

Suggested intermediate ranges for the ELF test scores include 7.8 to 10.5 (Byrne et al. 2018) or 7.7 to 9.7 (McDonald et al. 2018).

Clinical experts advised that indeterminate results are also possible from ARFI, although the exact values depend on the device manufacturer.

In current practice, biopsy may be considered for patients with these results to determine the extent of fibrosis. MRI-based testing could be used as an additional test for further investigation to help assess the need for a liver biopsy.

4.1.2 People for whom transient elastography or ARFI is unsuitable to assess fibrosis

People with NAFLD and an indeterminate result from FIB-4 or NFS (as described above) would be referred for transient elastography, ARFI, or the ELF test to further assess the degree of fibrosis.

However, transient elastography and ARFI may not be suitable for people with very high BMI or with significant ascites. The devices may fail, or clinicians may decide not to do transient elastography or ARFI because they are likely to fail.

Liver biopsy may be considered for patients in this category to determine the extent of fibrosis. MRI-based testing could be used as an additional test for further investigation to help assess the need for a liver biopsy.

4.1.3 People with *discordant results from fibrosis testing*

As noted in section 3.2.2.2, people may have multiple second-line tests for fibrosis (for example, transient elastography and ELF test) in order to confirm the presence of advanced fibrosis. In the case of discordant results between these tests, the EASL recommends considering liver biopsy to determine the extent of fibrosis (EASL 2021).

MRI-based testing could be used as an additional test for further investigation to help assess the need for a liver biopsy in this population.

5 Comparator

In current practice, people in the populations specified in section 4.1 would have no further testing to inform decisions about whether to do a liver biopsy, or any other aspect of their care. Clinical experts commented that probability of biopsy in these populations is based on clinical suspicion of advanced fibrosis, and characteristics such as age, weight and comorbidities.

6 Scope of the assessment

Table 1: Scope of the assessment

Decision question	Does the use of MRI based technologies for the assessment of non-alcoholic fatty liver disease represent a cost-effective use of NHS resources?
Populations	People with NAFLD for whom advanced fibrosis or cirrhosis has not been diagnosed: • Who have indeterminate results from fibrosis testing • For whom transient elastography or ARFI is unsuitable to assess fibrosis • Who have discordant results from fibrosis testing **Subgroups** If data permit, subgroup analyses could be done: • Based on which prior tests for fibrosis have been done • For children or young people
Interventions	• LiverMultiScan • Magnetic resonance elastography
Comparator	No further testing prior to a decision about whether to do a biopsy or any other aspect of care
Reference standard	Liver biopsy (see section 3.2.2.6)
Healthcare setting	Secondary or tertiary care
Outcomes	Intermediate measures for consideration may include:

	• Test accuracy for:
	  ○ fibrosis
	  ○ inflammation
	  ○ steatosis
	• Impact of test result on clinical decision making (such as whether a biopsy is done, frequency of subsequent monitoring, lifestyle advice or intervention offered)
	• Prognostic ability (for example, to predict progression of fibrosis or clinical outcomes)
	• Number of liver biopsies
	• Uptake and maintenance of lifestyle modifications
	• Time to receive test results
	• Time to diagnosis
	• Test failure rate
	• Reduction or remission of liver fibrosis or fibro-inflammation
	• Reduction of liver fat

	Clinical outcomes for consideration may include: • Mortality • Morbidity (can be liver-related and non-liver related, and including from complications related to liver biopsy)
	Patient-reported outcomes for consideration may include: • Health-related quality of life • Acceptability of different testing modalities
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Costs related to doing the tests, including staff time for testing and interpretation • Cost of treatment (including treatment of any adverse events caused by liver biopsy) • Cost of monitoring • Training costs, including staff time
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year (ICER).
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

7 Other issues for consideration

7.1 Assessment of liver steatosis

MRI-PDFF is offered as part of the LiverMultiScan package in order to quantify and visualise fat. MRE does not measure fat but can be used alongside MRI-PDFF protocols offered by MRI scanner manufacturers to assess steatosis in the same session. Clinical experts have advised that the level of steatosis is not generally used to inform clinical decision making with people with NAFLD in the NHS. However, quantitative assessment of fat from MRI-based tests can be motivational for people and helps to monitor the effect of interventions such as lifestyle management on reducing fat levels.

7.2 Future therapies

There are currently no therapies approved for the treatment of liver fibrosis, NAFLD or NASH, although NICE recommends off-label use of pioglitazone or vitamin E in people with advanced fibrosis. Multiple drugs for NASH are in Phase 3 or 4 trials and may be approved in the future (Campbell et al. 2021).

7.3 Variability in liver fibrosis testing in the NHS

As described in section 3, tests used for liver fibrosis across the NHS vary considerably. As such, the tests done prior to MRI-based tests at the proposed position for assessment may vary in practice, and also in any studies assessing use of these tests. If possible, subgroup analysis based on the tests done prior to use of the MRI-based tests in studies should be done to determine if this has any impact on performance or impact on outcomes.

8 Potential equality issues

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

People of South Asian origin may have a more centralised distribution of body fat, leading to a higher risk of associated chronic diseases such as NAFLD or NASH (De Silva et al. 2018; British Liver Trust, 2018). Criteria for suspected NAFLD or NASH may be different in the South Asian population than in the wider population. According to the British Liver Trust, a BMI above 23 kg/m^2 is considered to increase the risk of NAFLD in people of South Asian origin. Similarly, a recommendation was made to reduce the healthy waist circumference range for men in this population, from 94 cm to 90 cm (British Liver Trust, 2018).

One of the major risk factors for NAFLD is obesity. Transient elastography or ARFI may fail in people with obesity due to fat or fluid overlying the liver. Therefore, MRI techniques may be beneficial for people who are obese if they enable non-invasive characterisation of fibrosis where other techniques may not work. However, MRI techniques may not be suitable for people with a very high BMI because of the size of the scanner bore.

9 Potential implementation issues

The main challenge to implementation of MRI-based assessments of liver fibrosis is the current high demand for MRI, and consequently the impact on radiographers and radiologists' capacity across the NHS.

A 2020 report from an independent review of diagnostic services for NHS England recommended the establishment of community diagnostic hubs. These centres would be in high street or retail park locations and would expand access to diagnostic technologies, including MRI. Some community diagnostic hubs have already been set up, but many are still in the planning and consultation stages in their local NHS trusts.

9.1 Effect of the COVID-19 pandemic

The COVID-19 pandemic has caused increased wait times for many in-hospital tests such as MRI and ultrasound. Although wait times are gradually returning to pre-pandemic levels (NHS England, April 2021), access to these services may still be restricted. Increasing the number of people referred to MRI for liver imaging will further increase wait times.

People with NAFLD and NASH may be at greater risk of infection and hospitalization for COVID-19 than the general population (Portincasa et al. 2020; Roca-Fernández et al. 2021).

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Appendix A Glossary of terms

ARFI is an ultrasound technique that applies a shear wave laterally to the usual ultrasound pulse. It is used to measure liver stiffness.

Ascites is a condition in which fluid collects in spaces in the abdomen.

Children are people up to 12 years old.

Cirrhosis is severe scarring of the liver, preventing normal liver function.

The **ELF test** is a proprietary blood test that measures three markers of fibrosis that are not normally evaluated in primary care tests: Hyaluronic acid, procollagen III amino-terminal peptide and tissue inhibitor of matrix metalloproteinase 1.

Fibrosis is the accumulation of scar tissue and may be caused by a variety of conditions.

Hepatic encephalopathy is a complication of cirrhosis in which toxic substances enter the brain and cause cognitive symptoms.

Metabolic syndrome is a term for the combination of diabetes, high blood pressure and obesity.

NAFLD is a term for a range of conditions caused by a build-up of fat in the liver.

NASH is an advanced form of NAFLD in which accumulation of fat causes inflammation and changes the structure of liver cells. This can lead to fibrosis and eventually cirrhosis.

Perisinusoidal space is the space between hepatocytes and liver sinusoidal capillaries, usually filled with plasma.

Pioglitazone is a drug for type 2 diabetes that reduces insulin resistance.

The **portal vein** is the blood vessel carrying blood from the gastrointestinal tract, gall bladder, pancreas and spleen to the liver.

T1 and **T2*** are time constants (measured in milliseconds) describing the decay of a magnetic resonance signal.

Transient elastography evaluates liver stiffness by measuring the speed of a vibration generated on the skin using an ultrasound probe. It can also be used to measure liver fat.

Varices are enlarged veins caused by increased blood pressure, which can be caused by liver disease.

Young people are between 12 and 17 years old.

Appendix B Abbreviations

ALT	Alanine aminotransferase
ARFI	Acoustic radiation force impulse
AST	Aspartate aminotransferase
BMI	Body mass index
BSG	British Society of Gastroenterology
CCG	Clinical commissioning group
COVID-19	Coronavirus disease 2019
cT1	Iron-corrected T1
EASL	European association for the study of the liver
ELF	Enhanced liver fibrosis
FIB-4	Fibrosis-4 index
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NFS	NAFLD fibrosis score
PDFF	Proton density fat fraction
T1	Longitudinal relaxation time
T2	Transverse relaxation time
TE	Transient elastography

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