NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics consultation:

FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE diagnostics advisory committee (DAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Patient organisation submission** – British Liver Trust
7. **EAC correspondence log and collated expert questionnaires** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT562 FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care

External Assessment Centre report

Produced by: Newcastle External Assessment Centre (EAC)

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Number of attached appendices: 5

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

None.

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
ALD	Alcoholic liver disease
ALT	Alanine transaminase
APRI	Aspartate transaminase to platelet ratio index
ARPI	Acoustic radiaton force impulse
AST	Aspartate transaminase
AUDIT	Alcohol use disorders identification test
BMI	Body mass index
BSG	British Society of Gastroenterology
CAP	Controlled attenuation parameter
CAPc	Continuous controlled attenuation parameter
CCG	Clinical commissioning group
CHEERS	Consolidated Health Economic Evaluation Reporting
CI	Confidence interval
CT	Computerised tomography
DHSC	Department of Health and Social Care
DSA	Deterministic sensitivity analysis
EAC	External Assessment Centre
ELF	Enhanced liver fibrosis
FIB-4	Fibrosis-4 index for liver fibrosis
GBP	Pound Sterling
HA	Hyaluronic acid
HRG	Health Resource Group
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines and Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcohol related steatohepatitis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE Clinical Guideline
NICE MTG	NICE Medical Technology Guidance
NICE QS	NICE Quality Standard
NNS	Number needed to screen
NR	Not reported
P3NP	Procollagen 3 N-terminal peptide
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probability sensitivity analysis
PSSRU	Personal Social Services Research Unit
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
RSP	Risk stratification pathway
SCD	Skin to capsule distance
SD	Standard deviation
TE	Transient elastography

VAS	Visual analogue scale
Vs	Versus
VCTE	Vibration controlled transient elastography

Executive summary

In this assessment report, “Company” refers to Echosens. “EAC” refers to the Newcastle External Assessment Centre, the authors of this assessment report. “Clinical experts” refers to individuals, approved by NICE, who advised the EAC in the preparation of this report.

FibroScan is a device that performs a transient elastography test using ultrasound in the detection of liver fibrosis and cirrhosis. A number of models of FibroScan are currently available, and there is wide variability in referral criteria in current NHS practice for transient elastography measurement in secondary care. There is no current national guidance to support the use of FibroScan outside a hospital setting. The benefits of use in primary care claimed by the Company include earlier detection and treatment of liver disease, leading to avoidance of referrals to secondary care.

The Company identified 7 papers from their literature search; the EAC considered 3 of these as out of scope and identified an additional 15 papers from an independent search. In total, 19 publications from UK-based studies were included in the clinical evidence review, including 9 peer-reviewed publications (1 RCT, 5 cross-sectional, 2 cohort and 1 qualitative study), and 10 non peer-reviewed abstracts; five publications were from the Nottingham Community Liver Biomarkers Cohort study, and two publications were from the LOCATE study. The included evidence was heterogeneous in nature and differed in population screened (diabetes, obesity, alcohol, hepatitis risk factors) and setting (GP, drug or alcohol clinics, homeless hostel, community clinics, pop-up clinics).

The EAC identified no published evidence that directly compared FibroScan in a primary or community setting with FibroScan conducted in a secondary or specialist setting (in line with the final scope). However, clinical experts advise that proportions attending for liver assessments (using FibroScan) in a primary or community care setting exceed those in secondary care. The results demonstrated successful use of FibroScan outside a hospital setting, but also demonstrated wide variability in liver assessment uptake (between 38% and 97% depending on setting). Some papers reported test failure and unreliable test results, which may be related to the device or probe availability,

limited user experience with the technology, or patient habitus. None of the papers reported adverse events directly associated with FibroScan. Based on the clinical evidence, the EAC considers it plausible that more patients may attend an appointment for elastography if available outside a secondary or specialist care setting, leading to increased detection and management of liver fibrosis in a primary or community care. However, the impact on referrals to secondary care are unclear due to variable thresholds and diagnostic pathways described in the literature. Observed variability in test-retest reliability of transient elastography may be important in deciding the optimum thresholds to apply to a referral pathway. There is no long-term evidence to demonstrate that the use of FibroScan in primary care decreases time to diagnosis, or improves downstream patient outcomes.

The Company's economic model, based on a decision tree, estimated that use of FibroScan outside a hospital setting would lead to a saving of £41.44 per patient compared with standard care (£139.65 outside hospital versus £180.71 in hospital; 95% CI of saving £12.66 to £71.44). The EAC replicated the Company's model, but identified that the Company had twice included the time required for hospital-based healthcare professionals to perform and interpret scans (once via a micro-costing and once via a bundled tariff cost). The EAC's base case found the use of FibroScan in a non-hospital setting to be marginally cost incurring by £29.36 (point estimate), driven by increased attendance at liver assessments in primary and community care, subsequently leading to increased referrals to hepatology and for behavioural interventions. The patient benefits of FibroScan in a non-hospital setting are not considered using the cost-consequence framework of MTEP and neither the Company's model nor the EAC's model assessed cost effectiveness.

Within the specific context of the decision problem, the EAC has identified no direct comparative evidence for the relative clinical effectiveness of FibroScan between the two settings, and has found that, per-patient, performing the scan outside a hospital setting may be marginally cost incurring. However, the EAC considers that, provided clinical equivalence is demonstrated, there may be wider economic and patient benefit associated with providing FibroScan outside a hospital setting, particularly if provided as part of an integrated liver assessment pathway with well-defined referral criteria.

1 Decision problem

The Company has not proposed any variation to the decision problem specified in the final scope (NICE MT562 Final Scope, 2021), Table 1.

Table 1: Scope of the decision problem

Decision problem	Scope	Proposed variation in Company submission
Population	People having a FibroScan to assess for liver fibrosis or cirrhosis (as per current NHS practice)	No variation
Intervention	FibroScan done outside secondary or specialist care (for example, GP or community services).	No variation
Comparator(s)	FibroScan done in secondary or specialist care.	No variation
Outcomes	The outcome measures to consider include: • Test accuracy • Agreement between measurement made by FibroScan done in primary and secondary or specialist care • Comparative performance between different FibroScan models • Test failure • Uptake of offered FibroScan test • Uptake of behaviour or lifestyle change intervention • Number of referrals to secondary care • Number of people referred to alcohol or weight management services • Severity of liver fibrosis • Device-related adverse events • Use of NHS services (for example, GP or outpatient appointments) • Mortality • Morbidity (such as liver cirrhosis, liver related complications, cardiovascular complications)	No variation
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different	No variation

	numbers and combinations of devices are needed.	
Subgroups to be considered	Use of FibroScan in specific populations, for example for people with: • Non-alcoholic fatty liver disease • Suspected non-alcoholic fatty liver disease (for example, people with metabolic syndrome or type-2 diabetes) • Alcohol-related liver disease • Suspected alcohol-related liver disease (for example, based on hazardous alcohol use) • Hepatitis	No variation
Special considerations, including those related to equality	FibroScan may have higher failure rates in people with higher BMI, particularly for people with central obesity, where possible data reporting failure rates in this group should be extracted. People from Black African, African Caribbean and South Asian (Indian, Pakistani, Bangladeshi) backgrounds are at a higher risk of developing type 2 diabetes from a younger age and therefore have a higher risk of liver disease. People with alcohol or substance misuse are at higher risk of liver disease. Liver cirrhosis may in the long term, prevent a person from performing their normal day-to-day activities. Disability is a protected characteristic under the Equality Act 2010.	Company quantified higher BMI as 40 or higher. No variation
Abbreviations: BMI		

The EAC has made the following clarifications on other aspects of the scope.

- Population: patients with defined risk factors including paediatric patients.

- Intervention: includes any model of FibroScan (including portable models) used in any non-hospital setting (for example within primary care or community setting).

- Comparator: includes any model of FibroScan (including portable models) used in a hospital setting (for example secondary or specialist care).

2 Overview of the technology

FibroScan (Echosens) is a non-invasive class IIa medical device, with the first model CE marked in 2003, with valid certification provided by a Notified Body until 2024. FibroScan uses proprietary vibration controlled transient elastography (VCTE) to assess liver fibrosis and cirrhosis by measuring the degree of liver stiffness and a proprietary controlled attenuation parameter (CAP) to assess hepatic steatosis.

Four models of the device were included in the Company clinical submission: FibroScan 630 Expert, FibroScan 530 Compact, FibroScan 430 Mini+, FibroScan 230 GO, Table 2. The Company has claimed equivalent mode of operation and indication for use for these four models to previous models that are no longer available (FibroScan 502, FibroScan 402). The Company claims that the core components of the system have equivalent performance and safety between models, and that FibroScan models with latest software (CLPC 4.1) are equivalent to those using earlier software. The Company provided a summary table of technical, clinical and biological equivalence between models (EAC Correspondence Log, 2021). The Company based the table on Clinical Equivalence Reports (CERs) written for the purpose of conformity assessment (copies of these were provided to the EAC). For clinical equivalence, the Company reported no differences between models apart from certain features being available only in particular models. The Company did not provide any direct evidence for diagnostic accuracy equivalence between models additional to that reported in the literature.

Table 2: FibroScan models

Model	Portable/Cart-based	Screen	Weight	Core component	Software system	VTCE	CAP
FibroScan 630 Expert	Cart-based (mains power)	Dedicated computer within device	46 kg	Elastography engine (PV3)	CLPC 4.1	✓	✓
FibroScan 530 Compact	Cart-based (battery)	Dedicated computer within device	10 kg	Elastography engine (PV3)	CLPC 4.1	✓	✓
FibroScan 430 Mini+	Portable (battery)	Dedicated computer within device	5 kg	Elastography engine (PV3)	CLPC 4.1	✓	✓
FibroScan 230 GO	Portable (mains power)	Separate computer required (with internet access for user authentication and with FibroScan software installed)	5 kg	PV3 software (includes Acquisition Engine previously named Elastography Engine)	Fibroscan Application for end user computer interface (v0.4) Equipment software (v1.1)	✓	✓
FibroScan 502 [No longer available; sales stopped globally June 2015. Replaced by FibroScan 530]	Cart-based (mains power)	Dedicated computer within device	41 kg	Elastography engine (PV2)	CLPC A.2.2	✓	✓
FibroScan 402 [No longer available; sales stopped globally Feb 2017. Replaced by FibroScan 430 Mini]	Portable (mains power)	Dedicated computer within device	8 kg	Elastography engine (PV2)	CLPC B.2.1	✓	×
FibroScan 430 Mini [No longer available; sales will be stopped in UK end 2021. Replaced by FibroScan 430 Mini+]	Portable (battery)	Dedicated computer within device	5 kg	Elastography engine (PV3)	CLPC 4.1	✓	×

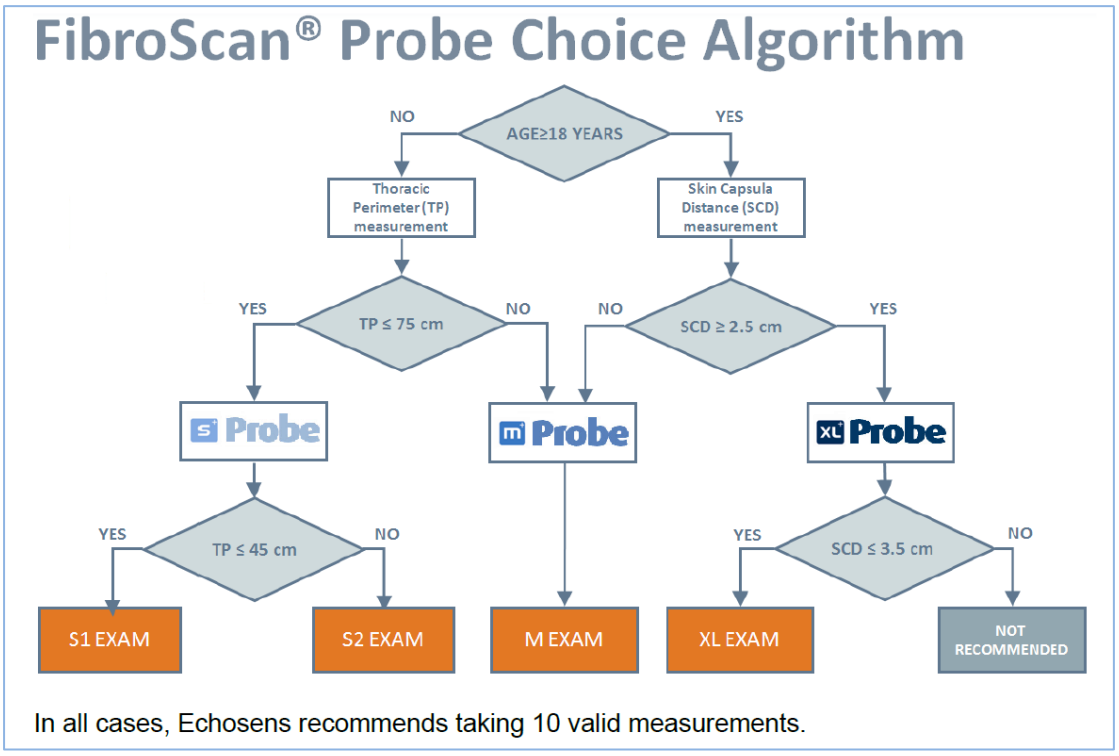
FibroScan comprises the following components:

- Main unit (mains or battery powered depending on model, cart or portable depending on the model),
- Single element ultrasound transducer probes. Three models available: S+, M+, XL+ with ultrasound centre frequencies of 5, 3.5 and 2.5 MHz respectively which can be used to conduct different examinations depending on patient morphology (Figure 1). Note that the S+ probe is not available with FibroScan 402.

  Using these probes, four different types of examination are available which correspond to specific measurement depth (such as liver's depth beneath the skin):

  - S1 exam: between 1.5 and 4 cm
  - S2 exam: between 2 and 5 cm
  - M exam: between 2.5 and 6.5 cm
  - XL exam: between 3.5 and 7.5 cm.

Figure 1: FibroScan probe choice algorithm (provided by the Company) based on thoracic perimeter (TP) and skin to capsule distance (SCD).



The transducer probe generates a transient vibration, which in turn generates an elastic shear wave at 50 Hz. Using VCTE the ultrasound transducer performs a series of ultrasound acquisitions to measure the speed (in m/s) of shear wave propagation and associated liver stiffness (in kPa). The range of measureable liver stiffness is 1.5 kPa to 75.0 kPa. All models of FibroScan conduct this measurement.

CAP is an optional measure of the attenuation of the ultrasonic signals (measured in dB/m) in tissue at a frequency of 3.5 MHz (regardless of the probe used). The Company launched SmartExam in 2021, which uses a new computation method of continuous CAP measurement (continuous CAP or CAPc) throughout the VCTE examination, and SmartDepth which enables automatic depth selection based on the patient's morphology. The Company claims that SmartExam permits deeper assessment of liver fibrosis and steatosis, extending probe to capsula distance from 35-75 mm to 45-85 mm when using the XL+ probe. SmartExam also automatically rejects measurements which do not meet validity criteria. The Company has confirmed the first generation CAP measurement is available on FibroScan 502, FibroScan 502 Touch, FibroScan 530 Compact, FibroScan 430 Mini/Mini+, FibroScan 630 Expert and FibroScan 230 GO, and that second generation CAPc measurement is available on FibroScan 502 Touch, FibroScan 530 Compact, FibroScan 430 Mini+, FibroScan 630 Expert and FibroScan 230 GO. The Company has confirmed that CAP can be measured with M+ and XL+ probes and that CAPc can be measured with all S+, M+ and XL+ probes.

3 Clinical context

All nine clinical experts advised that FibroScan is established practice in secondary care and no longer considered new (EAC Correspondence Log, 2021). Transient elastography conducted in secondary care setting is recommended in multiple NICE guidelines.

NICE's guideline on hepatitis B (chronic) (NICE CG165, 2017): Liver biopsy and transient elastography, done in a secondary care setting, are the most common methods of assessing fibrosis in people with chronic hepatitis B and

chronic hepatitis C in the NHS. Transient elastography is the first test recommended for liver disease in adults newly referred for assessment. Liver biopsy would be offered, or considered, based on the transient elastography score and age, alanine transaminase (ALT) level and hepatitis B viral load. Annual reassessment of liver disease using transient elastography would be offered to adults not taking antiviral treatment.

NICE's guideline on cirrhosis in over 16s (NICE NG50, 2016): Transient elastography is also recommended 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 (NAFLD) and advanced liver fibrosis. Liver biopsy should be considered for the diagnosis of cirrhosis in people when transient elastography is not available.

NICE's guideline on non-alcoholic fatty liver disease (NAFLD) (NICE NG49, 2016): Liver ultrasound is recommended to test children and young people for NAFLD. The enhanced liver fibrosis test should be used for people who have been diagnosed with NAFLD, to test for advanced liver fibrosis.

However, the Company have correctly highlighted that there are no NICE guidelines for assessing liver fibrosis and cirrhosis outside a secondary or specialist care setting. The clinical experts have also advised that the criteria for liver fibrosis and cirrhosis assessment in a primary and community setting are not well defined and are variable within the NHS (EAC Correspondence Log, 2021).

British Society of Gastroenterology (BSG) guidelines (Newsome *et al.* 2017) include a number of recommendations, which include FibroScan for the management of abnormal liver bloods tests in children and adults in both primary and secondary care:

- Recommendation 7: In adults with NAFLD, first-line testing includes FIB-4 or NAFLD fibrosis score. Second-line testing requires a quantitative assessment of fibrosis such as serum enhanced liver fibrosis (ELF) measurement, or FibroScan/acoustic radiation force impulse (ARFI) elastography).

- Recommendation 9: Harmful drinkers should undergo risk stratification with clinical assessment and FibroScan/ARFI. Adults should be referred to secondary care if there is evidence of advanced liver disease (features of cirrhosis or portal hypertension on imaging or from blood tests) and/or FibroScan reading >16 kPa (if available).

The Royal College of General Practitioners has made recommendations for commissioning bodies to improve the early detection of chronic liver disease in UK primary care; Recommendation 6: Test individuals with a high risk of alcohol or NAFLD related liver disease for fibrosis according to NICE and BSG guidelines, as follows:

- Alcohol risk identified as high (>50 units/week men of >35 units/week women or AUDIT-C positive [which is a shortened 3-item version of the 10-item Alcohol use disorders identification test (AUDIT) tool]:
  - Direct to FibroScan if available
  - If not available then direct to ELF testing
  - If neither available then referral to gastroenterology/hepatology
- NAFLD risk high (based on metabolic risk assessment of abnormal blood tests with no other cause identified or fat on ultrasound with no other cause identified):
  - Direct to ELF test if available (see NICE guidance)
  - Or serum based algorithm test (FIB-4, NAFLD fibrosis score, AST:ALT ratio) followed by FibroScan if available
  - If neither ELF nor direct access FibroScan are available to request from primary care, then referral on the bases of an indeterminate FIB-4, NAFLD Fibrosis score or high AST/ALT ratio to gastroenterology/hepatology.

Special considerations, including issues related to equality

FibroScan is contraindicated for use on an organ other than the liver (eyes and mucosa must be avoided), on wounds. The instructions for use provided

by the company for FibroScan 230 GO (dated July 2021) state additional contraindications related to patients with active implants such as pacemakers, defibrillators, pumps, and on pregnant women; however during fact check the company has clarified that this statement only applies in the US and Japan.

The S+ probe is not approved for patients over 18 years old, the M+ probe is not approved for patients under 14 years old and the XL+ probe is not approved for patients under 18 years old.

There are different types of liver diseases that 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 time, leading to long-term conditions. This may mean someone becomes 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 2010.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The Company search strategy was peer reviewed using the PRESS tool (McGowan *et al.* 2016), Appendix A1. The Company's search strategy for clinical evidence addressed appropriate basic concepts that warranted inclusion: FibroScan, liver and primary care. However, there were several issues. First, the range of sources could have been broader – therefore, an expanded range of sources was used in the EAC literature search. Secondly, there was scope for using significantly more synonyms and alternatives for FibroScan and particularly for primary care (which might be referred to in quite a range of ways without using that exact phrase in the title and abstract). Thirdly, some of the alternatives used were irrelevant – "Vibration Controlled Transient Elastography" would be covered by "Transient Elastography", and all other liver terms would be covered by the All Fields "liver" term.

A literature search was developed by the EAC, using the concepts: [FibroScan] AND [primary care] AND [UK]. FibroScan is used almost exclusively for assessing livers, so the qualifying concept of 'liver' was only applied to the less specific terms used for transient elastography, which was used as an alternative to FibroScan. Other synonyms for FibroScan included

model numbers, the Company name, and the values that FibroScan measures.

The primary care terms were developed starting from a published filter (Pols *et al.* 2015), taking some elements from both the sensitive and specific versions of the filter, and expanding with additional terms particularly relevant to this assessment. Terms used included general practice, community care, and staff roles (covering those who might be conducting FibroScan tests in a primary care environment).

One additional element not included in the Company search was to specify the UK as location. Given the nuance of this assessment's focus on the potential change of context for FibroScan use from secondary to primary care (and associated factors like who would conduct the readings in the primary care context, their experience in doing so, and facilities required), results from outside the UK – where health service provision may not be structured in the same way – were deemed not in scope. Once this was confirmed, to most comprehensively identify UK results, validated Medline and Embase filters were used (Ayiku *et al.* 2019) and adapted for other databases where possible).

The search strategy was developed in Embase and tested using several preliminarily identified relevant papers. The strategy was then translated into other relevant databases (described in Appendix A2). The searches were run on 30th September 2021 on Medline (Ovid), Embase (Ovid), CINAHL (EBSCOhost), Cochrane Database of Systematic Reviews (CDSR) and CENTRAL (Cochrane Library via Wiley), INAHTA, Clinicaltrials.gov, WHO ICTRP, IDEAS/RePEc and NHS Economic Evaluation Database (NHSEED). A total of 498 results were initially retrieved, of which 410 remained after deduplication.

The title and abstract of each were sifted according to the final scope (NICE MT562 Final Scope, 2021) by a single reviewer. Papers with an undefined or non-UK setting were excluded. Full papers were retrieved and reviewed by a single reviewer. Included papers were reviewed by a second reviewer. For trials reporting results in multiple conference abstracts, the most recent was selected. Note that the EAC did not identify any papers which directly

compared FibroScan used in a primary or community care setting with FibroScan used in a secondary or specialist care setting. The EAC relaxed the comparator inclusion criteria (such as single-arm studies) due to those studies being relevant to some outcomes and having the potential to detect adverse events. The selection process is illustrated as a PRISMA diagram in Appendix A3.

4.2 *Included and excluded studies*

The Company identified a total of seven peer-reviewed publications they considered were relevant and within the scope of the decision problem. The EAC excluded three of these; two due to setting (one used FibroScan in a mixed primary and secondary care setting and did not report outcomes separately by setting, one used FibroScan exclusively in a tertiary centre) and one systematic review which combined all non-invasive markers of liver fibrosis (the EAC reviewed all primary evidence using transient elastography), Table 3.

The EAC identified a total of nine peer-reviewed publications and ten conference abstracts relevant to the decision problem, Table 4, only four of which were included in the Company submission, Table 5. Note that the Company identified but excluded one of the publications included by the EAC due to its small sample size (fewer than 100 patients), which fell below their threshold for inclusion. A total of 19 papers are included in this assessment report.

Table 3: Studies included by Company and excluded by the EAC

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Mansour *et al.* (2021) UK	Cohort study (n=466; FibroScan used in 54) FibroScan FS402. FibroScan FS502 with XL+ probe used in patients with BMI greater than 35 kg/m^2. ☑ Patients considered high risk of advanced fibrosis (FIB-4 greater than 1.3 for those aged 65 years and younger, greater than 2.0 for those aged 65 years and older) were offered transient elastography. Patients with severe frailty or life-limiting conditions were not offered transient elastography. Patients with liver stiffness greater than or equal to 8 kPa were referred to secondary care (liver aetiology screen and ultrasonography where appropriate). Further interventions (biopsy) at discretion of reviewing clinician/patient. ☑	Patients aged 35 years and older, with type 2 diabetes attending annual review between April 2018 and September 2019 at two primary care practices had FIB-4 score requested in addition to routine blood tests. ☑ Multi-centre (transient elastography conducted at primary care centre or at local hospital). ☒	Number of patients identified with advanced fibrosis or cirrhosis, service uptake, liver stiffness, scan failure/unreliable scan, advanced liver disease (radiological evidence of cirrhosis, oesophageal or gastric varices on endoscopy, F3 or F4 fibrosis on livery histology following review in specialist clinic, diagnosis of cirrhosis based on overall clinical assessment). ☑	Mixed setting - combines intervention and comparator with results not reported separately for each. [Patients were either scanned at their primary care centre or local hospital; results suggest 35 patients were offered scan at GP, and 16 in secondary care, however unclear of care in the remaining 7 patients].
Rhodes *et al.* (2021) UK	Retrospective cross-sectional study of consecutive patients (n=762; FibroScan used and gave valid reading in n=575). FibroScan (model not reported) considered diagnostic for	Patients aged 18 years and older newly referred from primary care to a hospital-based hepatology service with a suspected diagnosis of alcohol-related liver disease or non-alcoholic fatty liver disease or where the GP specified that patient	Proportion of referrals that had advanced fibrosis (deemed necessary referrals, by a liver specialist, and could be discharged back to ongoing care in the community),	Setting - FibroScan used in tertiary centre.

	advanced fibrosis if greater than or equal to 11 kPa in alcohol-related liver disease, and greater than or equal to 10 kPa in non-alcoholic fatty liver disease. ☑ FIB-4 and APRI scores were calculated using blood tests from the first attendance to clinic after referral.	had steatosis or chronic liver disease on ultrasound in combination with mention of metabolic risk factors (BMI greater than or equal to 25, diabetes, high waist circumference, high cholesterol or hypertension) between January 2015 and January 2018. Patients with any other hepatological diagnosis made prior to referral (including but not limited to auto-immune hepatitis, viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular carcinoma) were excluded. ☑ Single-centre (advanced fibrosis assessed by tertiary centre hepatologists using combination of FibroScan, imaging, examination, blood tests and liver histology where available). ☒	prevalence of both alcohol and fatty liver disease.	
Harris *et al.* (2017) UK	Systematic review (N=19, transient elastography used in 12 studies). Interventions: non-invasive tests for liver fibrosis ☒☑	Embase, Medline and Web of Science searches up to 2015, UK and worldwide conferences between 2010 and 2015. Studies were included if patients were aged 18 years and older, non-hospital setting (community, primary care or outreach unit), underwent a validated non-invasive test which would stratify for liver fibrosis, prevalence of clinically significant	Screening uptake, prevalence of fibrosis, prevalence of cirrhosis, liver biopsy, alanine aminotransferase concentration. ☑	Intervention: combined results from all non-invasive tests for liver fibrosis. Systematic review excluded, however primary evidence reporting transient elastography as intervention reviewed separately: Wong *et al.* (2012) - setting unclear: “clinic visit”, but

		liver disease (either liver fibrosis or cirrhosis) reported as an outcome measure (histopathology validation was not an absolute requirement), and study participants were recruited from an unselected population or on the basis of the participants' age, or a defined risk factor for alcoholic liver disease or non-alcoholic fatty liver disease. Studies were excluded if population, setting where the non-invasive test was carried out or threshold for the non-invasive test were not adequately reported. Studies were also excluded if the participants were solely investigated for liver disease other than alcoholic liver disease or non-alcoholic fatty liver disease (for example, viral hepatitis) or if they were not published in English. ☒☑		author affiliations are hospitals. You *et al.* (2015) – secondary care: "Severance Hospital". Lemoine *et al.* (2014) – specialist care: recruitment in community but FibroScan used in "Medical Research Council Laboratories". Malik *et al.* (2009) – setting unclear: recruitment in community, but location of "liver health screening check" not reported. Fabrellas *et al.* (2013) – "nurse consultancy specifically set up for the study" in primary care clinic (Spain) Poynard *et al.* (2010) – secondary care: initial test with FibroTest (different intervention) in community, reinvestigation with FibroScan by experienced hepatologists, and ultrasound, endoscopy or biopsy. Roulot *et al.* (2011) – social medical centre (France)

				Morling *et al.* (2014) – setting unclear: elastography conducted at year 4 follow-up visit only. Das *et al.* (2010) – likely secondary care: first phase screening in community, second and third in "institute". Moessner *et al.* (2011) – regional treatment centres for drug users (Denmark). Harman *et al.* (2015) - included: patients with high simple biomarker result underwent transient elastography at the community practice Baba *et al.* (2011) - likely secondary care: corresponding author affiliated with social insurance hospital.
Key: ☑ aspect of study in scope; ☒ aspect of study not in scope ☑☒ aspect of study partially in scope, or elements of this are not in scope. Abbreviations: APRI, AST to platelet ratio; BMI, body mass index; FIB-4, Fibrosis-4 index for liver fibrosis				

Table 4: Studies selected by the EAC as the evidence base

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
LOCATE study	El-Gohary *et al.* (2018) UK	Prospective cluster randomised feasibility trial (n=26,838 eligible in intervention arm, and n=26,236 eligible in control arm; 7,183 in intervention arm identified for further investigation, only 910 attended liver clinic). GP practices were amongst those with the highest rates of hospital liver admissions in preceding years, randomisation of practices at 1:1 ratio without matching. Intervention: nurse-led clinical. Included blood pressure, BMI, waist circumference, blood samples (full blood count, liver function tests including aspartate transaminase, gamma-glutamyl transferase, and serum fibrosis markers hyaluronan and procollagen 3 N-terminal peptide) and portable FibroScan 402 device (median value less than 6 kPa no fibrosis, 6 to 8 kPa liver warning, 8 to 12.9 kPa progressive fibrosis, at least13 kPa probable cirrhosis). ☑	Patients aged 18 years or older recruited between July 2014 and March 2016. Patients unable to provide consent, known terminal illness, significant co-existing illness rendering participation difficult (housebound, undergoing cancer treatment), pre-existing liver disease documented in primary care records were excluded. Three subgroups recruited: 1) suspected cases opportunistically identified by GPs and nurses, 2) nurse-led case finding of subjects with specific risk factors (elevated liver function tests, alcohol misuse, or type 2 diabetes), 3) population screening for excess alcohol with a minimum AUDIT questionnaire score of 8. ☑ Multi-centre (10 urban GP practices in single city). ☑	Attendance at clinic for testing, proportion of patients with liver disease (liver warning, progressive fibrosis, probably cirrhosis) ☑	Mixed intervention as part of screening for liver disease (FibroScan results combined with blood samples and physiological factors). Comparator represents standard of care (lack of targeted screening for liver fibrosis/cirrhosis) and may include patients referred to secondary care for transient elastography. Results from comparator arm are not in line with final scope.

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		Comparator: standard care ☒☑ Patients with evidence of liver fibrosis (probably cirrhosis, progressive fibrosis, liver warning) regardless of subgroup were assessed in virtual combined clinic by a GP and consultant hepatologist. Patients did not undergo biopsy to confirm diagnosis. GPs were asked to refer patients diagnosed with cirrhosis, for an upper GI endoscopy in hospital. Where the diagnosis was uncertain or where secondary care treatment was required it was suggested to GPs that they refer the subject to hepatology at the hospital for further care or assessment. Where further tests were required a second or third virtual review was performed.			
LOCATE study	Reinson *et al.* (2021) UK	Follow-up study of the intervention arm (n=910 who initially attended liver clinic) from a prospective cluster randomised trial; mean (SD)	Patients from initial LOCATE intervention, alive, who had agreed to be contacted for follow-up with baseline vibration –controlled transient	Attendance at follow-up clinic for rescan,	Subgroup of El-Gohary *et al*. (2018) study. However provided long-term

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		time interval between baseline and follow-up scans 53.6 (3.4) months. Intervention (n=116 agreed to take part): nurse-led community liver service. FibroScan Mini+ 430 and FibroScan 402 were used in n=59: (median value less than 6 kPa no fibrosis, between 6 kPa and 8 kPa liver warning, between 8 kPa and 12.9 kPa progressive fibrosis, 13 kPa and above: presumed cirrhosis). Patient weight and alcohol AUDIT questionnaire ☑ Patients whose follow-up reading was above 10kPa were referred to secondary care Hepatology clinic.	elastography of at least 6 kPa, and less than 12 kPa. Two recruitment methods were used to invite patients for a rescan: 1) the study team wrote to the GP of all eligible patients to ask them to refer to the community liver service, 2) eligible patients were telephoned between August 2019 and May 2020. ☑ Multi-centre (two primary care sites in single city). ☑	change in liver fibrosis stage. ☑	outcomes not captured elsewhere.
Nottingham Community Liver Biomarkers Cohort (NCT02037867)	Harman *et al.* (2018) UK: Nottingham	Prospective cross-sectional study (n=2022, FibroScan used in 919) Intervention: initial screening blood marker prior to transient elastography. FibroScan FS402 with M+ probe used in patients with BMI less than 35 kg/m^2 in general practice setting.	Patients aged 18 years and older, with selected risk factors for lifestyle related chronic liver disease (hazardous alcohol use, type 2 diabetes, persistently elevated serum alanine aminotransferase) identified from general medical practice electronic patient records, recruited between February 2012	Test uptake, test failure (inability to obtain ten valid liver stiffness measurements), unreliable test results (liver stiffness at least 7.1kPa and IQR or median ratio	Mixed intervention as part of screening for liver disease (blood markers prior to FibroScan, diagnosis in combination with histology, endoscopy and ultrasound).

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		FibroScan FS502 device with XL+ probe used in hospital setting in patients with BMI at least 35 kg/m^2 or with initial failed liver stiffness acquisition using the M+ probe. ☒☑ Threshold of 8.0 kPa used to define elevated liver stiffness and clinically significant liver disease. Further investigations (ultrasound, liver biopsy, endoscopy) arranged on case-by-case basis by a visiting consultant hepatologist in the community. Diagnosis of cirrhosis also by visiting consultant hepatologist, and not based on FibroScan results alone, used in combination with histology, endoscopy, ultrasound.	and September 2014. Patients with definitive evidence of hepatic fibrosis or cirrhosis from previous investigations, contraindication to transient elastography (pregnancy, indwelling cardiac device), metastatic malignancy, and those unable to provide consent or housebound and unable to attend the practice, were excluded. Patients who presented with symptoms of decompensated liver cirrhosis (jaundice, variceal bleeding, ascites) were excluded and triaged straight to urgent hospital-based care, rather than screening with transient elastography in primary care. ☑ Multi-centre (four GP practices in single city; two located in affluent suburban borough, two situated in predominantly deprived areas) ☑	greater than 0.3), cirrhosis diagnosis categorised as alcoholic liver disease (if hazardous alcohol use was present in the absence of obesity or Type 2 diabetes), or non-alcoholic fatty liver disease (in the presence of type 2 diabetes or obesity but without hazardous alcohol use) and dual aetiology (if a combination of hazardous alcohol use and type 2 diabetes or obesity were present). ☑	The study also reports on the number of patients with diagnosis of liver cirrhosis in the population prior to the study commencement who were excluded from the study (diagnosis made using standard care), however duration of this is not well reported.
Nottingham Community Liver Biomarkers	Harman *et al.* (2015)	Prospective cross-sectional study (n=504, FibroScan used in 378)	Patients aged 18 years and older, with selected risk factors for lifestyle related chronic liver disease (hazardous alcohol use,	Test uptake, unreliable test results (at least 7.1 kPa and IQR	Mixed intervention as part of screening for liver disease (blood markers prior to

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Cohort (NCT02037867)	UK: Nottingham	Intervention: initial screening blood marker prior to transient elastography. FibroScan FS402 with M+ probe used in patients with BMI less than 35 kg/m^2 in community practice setting. FibroScan FS502 device with XL+ probe used in hospital setting in patients with BMI at least 35 kg/m^2 or with initial failed liver stiffness acquisition using the M+ probe. ☒☑ Threshold of 8.0 kPa used to define elevated liver stiffness and clinically significant liver disease. Patients with high liver stiffness results, including high but unreliable acquisitions, were reviewed by a visiting consultant hepatologist in the community. Further investigations (ultrasound, liver biopsy, enrollment into cirrhosis surveillance programmes) arranged on case-by-case basis. Cirrhosis was definitively diagnosed in all cases based on the established clinical, radiological (including transient	type 2 diabetes, persistently elevated serum alanine aminotransferase with negative serology) identified from general medical practice electronic patient records, recruited between February 2012 and April 2013. Patients with definitive evidence of hepatic fibrosis or cirrhosis from previous investigations, contraindication to transient elastography (pregnancy, indwelling cardiac device), metastatic malignancy, and those unable to provide consent or housebound and unable to attend the practice, were excluded. ☑ Multi-centre (two suburban GP practices in single city) ☑	or median ratio greater than 0.3), test failure, clinically significant liver disease, cirrhosis diagnosis, liver biopsy. ☑	FibroScan, diagnosis in combination with clinical, radiological and histological assessment). The study also reports on the number of patients with diagnosis of liver cirrhosis with normal liver enzymes which would have been missed using standard care.

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		elastography result) or histological assessment. ☑			
Nottingham Community Liver Biomarkers Cohort (NCT02037867)	Harris *et al.* (2019) UK: Leicester	Prospective cross-sectional (n=1023, FibroScan used in 576). Intervention: Portable FibroScan FS402 device (ten measurements obtained using M+ or XL+ probe) used in a community-based risk stratification pathway; significant liver disease defined as greater than or equal to 8.0 kPa.☑ Patients with significant liver disease were invited back to see a hepatologist (employed by a university hospital) in the primary care practice, where further investigations were organised if deemed appropriate.	Patients aged 18 years and older, with one or more lifestyle-related risk factors for chronic liver disease (hazardous alcohol use, type 2 diabetes, obesity), identified from electronic primary care records between January 2015 and March 2016. Patients with contraindication to transient elastography (pregnancy, implantable cardiac device), known diagnosis of chronic liver disease, known malignancy or other terminal illness, inability to consent or housebound and unable to attend the practice, were excluded. ☑ Single-centre (assumed all FibroScan measurements were conducted in primary care practice) ☑	Proportion of patients with significant liver disease, test uptake, number of patients with unreliable readings (fewer than ten measurements and an IQR or median ratio greater than 0.3), diagnosis of cirrhosis (using FibroScan, clinical acumen, radiology and endoscopy) ☑	Subgroups: suspected alcohol related liver disease, suspected non-alcoholic fatty liver disease.
Nottingham Community Liver Biomarkers Cohort (NCT02037867)	Harris *et al.* (2018) UK: Leicester	Test agreement between probes using subset of data from prospective cross-sectional study (n=477).	Patients aged at least 18 years, with one or more lifestyle-related risk factors for chronic liver disease (hazardous alcohol use, type 2 diabetes, obesity), identified from electronic primary	Test uptake, number of patients with valid measurements, number of unreliable	Subgroup: obesity main subgroup (some overlap with hazardous alcohol

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		Intervention: Portable FibroScan 402 device (ten measurements, with median value reported) used in a community-based risk stratification pathway; significant liver disease defined as at least 8.0 kPa. Measurement was attempted with both M+ and XL+ probes for all patients with BMI of at least 28.0 kg/m^2 ☑ From Harris *et al*. 2019: Patients with significant liver disease were invited back to see a hepatologist (employed by a university hospital) in the primary care practice, where further investigations were organised if deemed appropriate.	care records between January 2015 and March 2016. Patients with contraindication to transient elastography (pregnancy, implantable cardiac device), known diagnosis of chronic liver disease, known malignancy or other terminal illness, inability to consent or housebound and unable to attend the practice, were excluded. ☑ Single-centre (assumed all FibroScan measurements were conducted in primary care practice) ☑	readings (based on IQR or median ratio), correlation and mean difference in measurements obtained by two probes. ☑	use and type 2 diabetes).
Nottingham Community Liver Biomarkers Cohort (NCT02037867)	Knight *et al.* (2020) UK [Nottingham Community Liver Biomarkers Cohort: NCT02037867]	Qualitative study (n=20) Intervention: Portable FibroScan (model[s] not reported) ☑	Sampled from large cohort of patients who underwent stratification of chronic liver disease in the community using a portable transient elastography device (Harman *et al.* 2015). Sampling strata for invitation for interview were: 1) GP surgery location (suburban vs. inner city), 2) chronic liver disease risk factor (hazardous alcohol use or	Test acceptability, comprehension and impact of receiving transient elastography results. ☒☑	Small sample size, however provides insight into patient acceptability of screening intervention from a UK population.

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
			type 2 diabetes) and 3) diagnosis assigned after community liver disease stratification (normal liver stiffness vs. liver fibrosis vs. liver cirrhosis). Patients were excluded from interview selection if they were unable to communicate in English. Face-to-face interviews were conducted over a 6-month period with patients who had attended a transient elastography assessment between 6 months and 2 years before data collection. ☑		
Not reported	Matthews *et al.* (2019) UK: Edinburgh	Prospective observational pilot study (n=79) Intervention: portable FibroScan (model not reported) ☑ Participants with FibroScan reading not more than 7.0 kPa had lifestyle advice reinforced. Participants with reading of 7.1 kPa or higher were offered an appointment to attend an NHS nurse-led liver clinic within the same community service, on another day (bloods for full liver profile, platelets, HA, ALT,	Individuals aged over 16 years, with ability to provide informed consent, who were attending either the triage facility for assessment of their support needs, or who were currently undergoing alcohol support in the centre. Those with possibility of or known pregnancy, pacemaker, ascites, open wound close to right eighth to tenth intercostal margins, known cirrhosis and no alcohol history, were excluded. Recruitment between November 2014 and end of October 2015 (with	Acceptability of cirrhosis screening, onward referral to specialist liver services. ☑	

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		AST). Those with readings of 8.0 kPa or higher were referred for ultrasound and clinical evaluation by consultant hepatologist or senior registrar within hepatology team. Blood results of those with FibroScan results between 7.1 kPa and 8.0 kPa were discussed with consultant hepatologist to decide whether further investigations and medical assessment were required. Liver biopsy was not required to determine degree of chronic liver disease (none taken during study period).	screening via FibroScan offered for first 6 months). ☑ Single-centre (community alcohol support centre). ☑		
Not reported	Surey *et al.* (2019) UK: London	Observational study (n=295) Intervention: portable FibroScan (model not reported). Measurements taken by peer support workers. ☑ Patients testing positive for hepatitis C, previous positive results, or with risk factors of liver disease were offered FibroScan.	Participants aged over 16 years, willingness and ability to provide informed written consent, being from an underserved population in the community (including people who are homeless, people who misuse substances, and people exposed to the prison system). Patients were screened between September 2016 and May 2018 ☑ Multi-centre (63 sites in single city, including drug and alcohol	Liver fibrosis stages ☑	Main focus on paper is hepatitis C testing and pathway. Liver fibrosis stages reported only (no additional information provided).

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
			services, homeless day centres, homeless hostels) ☑		
Not reported	†Corrigall *et al.* 2018 UK: exact location not reported	Cohort pilot study (n=174) Intervention: FibroScan (model not reported), dried blood spot screening (hepatitis B, C and HIV serology, hepatitis C RNA, T-spot), referral to secondary care for initiation of approved direct acting antiviral therapy and ongoing management of any concomitant chronic liver disease. ☒☑	Over one year (August 2015 to 2016) onsite nurse-led consultation, counselling, screening and risk stratification. Multi-centre: five community drug and alcohol services ☑	Median FibroScan measurement, number of patients with results suggestive of cirrhosis. ☑	
Vulnerable Adults Liver Disease (VALID) study	†Hashim *et al.* (2019) UK: south east England	Cohort (n=127) Intervention: offered alcohol (AUDIT) questionnaire and substance misuse assessment, blood borne virus (BBV) testing, mobile transient elastography (FibroScan device and model not reported), and focused treatment. ☑ Clinically significant fibrosis defined as liver stiffness measurement of at least 8 kPa. Cirrhosis defined as liver	Liver service set up in October 2015. Consecutive individuals aged over 18 years. ☑ Multi-centre: two homeless hostels☑	Uptake, number of patients with clinically significant fibrosis and predictors, number of patients with cirrhosis and aetiological factors. ☑	

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		stiffness measurement of at least 13 kPa.			
Not reported	†Hosack *et al.* (2019) UK: West Berkshire	Prospective cohort (n=476) Intervention: transient elastography (FibroScan device and model not reported) conducted by hepatology specialist nurse. ☑ Referral to secondary care was advised in those with transient elastography score greater than 10 kPa. Patients were given lifestyle advice and signposted to appropriate community services (for example, drug and alcohol services, eat well services).	Risk factors prompting referral for transient elastography included type 2 diabetes, obesity, excess alcohol use. Recruited over 27 month period (dates not reported) ☑ Multi-centre: 4 GP practices ☑	Uptake, referral to secondary care, diagnoses. ☑	Unclear if those not undergoing transient elastography were due to uptake, failure of device or invalid results (not reported).
HepCATT study	†Irving *et al.* (2017) UK: exact location not reported	Before and after study (n=1232 patients) Intervention: range of activities aimed at increasing diagnosis and enhancing patient referral including educational initiatives, enhancement of peer support teams, introduction of dried blood spot testing, and integration of HCV assessment	People who inject drugs, attending drug treatment centre. 12 month intervention (exact dates not reported, but completed by January 2017). Single-centre: drug treatment centre ☑	Referral to hepatology, engagement (investigations including viral load and genotype, FibroScan, serum fibrosis markers or biopsy, consultation	Write up of results (before and after study) does not appear to match study design written in methods (non-randomised comparative study with sites assigned to intervention or control). Attendance

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		and treatment where possible. ☒☑		regarding treatment options). ☑	rates appear to refer to hepatology referrals
Not reported	†McGinley *et al.* (2017) UK: West Dunbartonshire	Retrospective observational study (n=179) Intervention: Portable FibroScan (model not reported). ☑	Data from patients referred into addiction and primary care clinics (between November 2012 and July 2016) were extracted from clinical database and electronic patient records. Multi-centre: addiction and primary care clinics☑	Uptake, change in behaviour, number of patients with F3 fibrosis or higher. ☑	No additional FibroScan results reported.
Not reported	†Mohamed *et al.* (2020) UK: Guildford and Woking	Cohort (n=124) Intervention: liver health assessed through FibroScan (model not reported) and hepatitis C antibody testing offered to all. ☑	Participants at venues hosting homeless populations between May and June 2020 (inclusive). ☑ Multi-centre: pop-up clinics. ☑	Average liver stiffness, average CAP values, further management, diagnosis of fibrosis and cirrhosis. ☑	Interpretation and influence of CAP values on diagnosis not reported.
Not reported	†Montague *et al.* (2020) UK: Lambeth, Lewisham, Soutwark	Qualitative, measuring patient acceptability of service model (n=35) Intervention: hepatitis C virus mobile outreach service including point of care finger prick screening and confirmatory testing, FibroScan	Homeless people. Exact recruitment dates not reported, but took place in 2018. ☑ Mobile outreach service (multiple locations) ☑	Patient acceptability. ☒☑	No FibroScan results reported.

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		(model not reported), MDT (including peer) and needle and syringe programme provision. ☑			
Project ITTREAT	†O'Sullivan *et al.* (2019) UK: south east England	Cohort (n=573) Intervention: offered dry blood spot testing, transient elastography (FibroScan device and model not reported), hepatitis C treatment. ☒☑	People who inject drugs. Exact recruitment dates not reported, but took place between 2013 and 2021. Single-centre: drug and alcohol treatment centre ☑	Uptake, stage of fibrosis ☑	Focus on hepatitis C detection and costs.
Not reported	†Roberts *et al.* (2015) UK: exact location not reported	Prospective cohort (n=189) Intervention: FibroScan (model not reported). ☑ Follow-up: - TE less than 8 kPa: 12 months - TE between 8 and 12 kPa: 6 months - TE between 12 and 20 kPa: 3 months - TE above 20 kPa: refer to hepatology clinic. Any clinical concern regardless of TE score was also referred.	Patients with no history of liver disease, never seen by gastroenterology or hepatology, referred from alcohol specialist nurses, alcohol assertive outreach team, specialist drug and alcohol services, or GP screening with AUDIT of 16 or higher, seen between November 2013 and February 2015. ☑ Single-centre: community clinic☑	Uptake, severity of liver fibrosis, referrals to hepatology, association between TE measurements and AUDIT scores ☑	Overlap in TE threshold categories. Assumed 7 patients with test failure.
Not reported	†Siu *et al*. (2019)	Cohort (n=49)	Over a 10 week period (dates not reported), hepatology specialist nurse attended the	Liver fibrosis severity, comparison with	

Study name (trial registration)	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
	UK: Aberdeen	Intervention: FibroScan (model not reported) and blood tests (NAFLD fibrosis, FIB-4, APRI). ☑ Clinically significant fibrosis (F2 or higher) was defined by LSM greater than 7 kPa, and advanced liver fibrosis/cirrhosis (F3 and F4) defined as LSM greater than 12 kPa. Patients with LSM greater than 7 kPa were given lifestyle modification advice (including diet, exercise, alcohol intake). Full "liver screen" was performed in these patients in a hepatology clinic, and follow-up FibroScan performed (time interval between initial and follow-up scan not reported).	type II diabetic clinic, unselected patients were given information leaflets before consenting to FibroScan and blood testing. ☑ Multi-centre: 3 GP practices ☑	liver fibrosis clinical scoring systems. ☑	

Key: ☑ aspect of study in scope; ☒ aspect of study not in scope ☑☒ aspect of study partially in scope, or elements of this are not in scope.

Abbreviations: ALT alanine aminotransferase; APRI AST to platelet ratio index; AST aspartate aminotransferase; AUDIT alcohol use disorders identification test; BBV blood borne virus; BMI body mass index; CAP Controlled Attenuation Parameter; FIB-4 Fibrosis-4 index for liver fibrosis; HA hyaluronic acid; HCV hepatitis C virus; IQR interquartile range; LSM liver stiffness measurement; MDT multidisciplinary team; NAFLD non-alcoholic fatty liver disease; RNA ribonucleic acid; TE transient elastography.

†Available as conference abstract only

Table 5: Papers included by Company and EAC

Author (year)	Included by Company	Included by EAC
†Corrigall *et al.* (2018)	No	Yes
El-Gohary *et al.* (2018)	Yes	Yes
Harman *et al.* (2015)	Yes	Yes
Harman *et al.* (2018)	Yes	Yes
Harris *et al.* (2017)	Yes	No
Harris *et al.* (2018)	No	Yes
Harris *et al.* (2019)	Yes	Yes
†Hashim *et al.* (2019)	No	Yes
†Hosack *et al.* (2019)	No	Yes
†Irving *et al.* (2017)	No	Yes
Knight *et al.* (2020)	No	Yes
Mansour *et al.* (2021)	Yes	No
Matthews *et al.* (2019)	No	Yes
†McGinley *et al.* (2017)	No	Yes
†Mohamed *et al.* (2020)	No	Yes
†Montague *et al.* (2020)	No	Yes
†O'Sullivan *et al.* (2019)	No	Yes
Reinson *et al.* (2021)	No	Yes
Rhodes *et al.* (2021)	Yes	No
†Robert *et al.* (2015)	No	Yes
†Sui *et al.* (2019)	No	Yes
Surey *et al.* (2019)	No	Yes
†Conference abstract		

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

The nine peer-reviewed publications included one cluster randomised feasibility study, five cross-sectional studies, two cohort studies, and one qualitative study. Seven of the nine publications relate to two trials.

Two publications relate to the local care and treatment of liver disease (LOCATE) study; a cluster randomised feasibility study (El-Gohary *et al.* 2018), and a cohort study (Reinson *et al.* 2021). Reinson *et al.* (2021) included a subgroup of the intervention arm who were followed-up for average of 54 months and had the transient elastography measurement repeated. Within LOCATE ten GP practices were randomised, without matching on practice characteristics, to standard care (control) or liver health nurse identifying patients via three pathways (intervention): suspected cases opportunistically identified by GP and practice nurses, nurse-led case finding of subjects with specific risk factors and population screening for excess alcohol use using the AUDIT questionnaire. Participants were then invited to a liver clinic (at their own GP practice) where blood samples (full blood count), liver function tests (aspartate transaminase (AST), gamma-glutamyl transferase (GGT)), serum fibrosis markers (hyaluronic acid (HA), amino terminal type III procollagen peptide (P3NP)), blood pressure, BMI, waist circumference and liver stiffness (using FibroScan) measurements were taken. Patients with evidence of liver fibrosis were assessed by GP and a consultant hepatologist; however, no liver biopsies were conducted to confirm findings. Longitudinal follow-up was in a subgroup of the intervention arm deemed “at risk” with a baseline transient elastography results greater or equal to 6 kPa and lower than 12 kPa.

Four cross-sectional studies (Harris *et al.* 2019; Harris *et al.* 2018; Harman *et al.* 2018; Harman *et al.* 2015) and the qualitative study (Knight *et al.* 2020) all reported subgroups of the Nottingham Community Liver Biomarkers Cohort study. The study identified patients at risk from electronic GP records and invited them to undergo transient elastography at their GP practice. There was overlap in patient recruitment dates between Harman *et al*. (2018)

recruiting February 2012 to September 2014, Harman *et al.* (2015) February 2012 to April 2013, and Knight *et al.* (2020) sampled from Harman *et al.* (2015), all recruiting from Nottingham. However, all three studies were included due to them reporting different outcomes. Two cross-sectional studies, Harris *et al.* (2019) and one that compared M+ and XL+ probe agreement (Harris *et al.* 2018) both reported different outcomes using a recruitment period of January 2015 to March 2016 in Leicester, hence their results are included and reported separately.

The remaining two peer-reviewed publications were conducted in a community alcohol support setting (Matthews *et al.* 2019) and in drug or alcohol services, homeless day centres and homeless hostels (Surey *et al.* 2019). Of the ten included abstracts, three were in a community drug or alcohol centre (*Corrgiall et al.* 2018; Irving *et al.* 2017, O'Sullivan *et al.* 2019), two were in pop-up or community clinics (Mohamed *et al*. 2020; Roberts *et al.* 2015), two were conducted in GP practices including one diabetic clinic (Hosak *et al.* 2019; Sui *et al.* 2019), one was conducted in both addiction and primary care clinics (McGinley *et al.* 2017), one was in a mobile outreach service (Montague *et al.* 2020), one was in a homeless hostel (Hashim *et al.* 2019).

5.2 *Critical appraisal of studies and review of Company's critical appraisal*

One cluster randomised controlled trial, described by the authors as a feasibility study (El-Gohary *et al.* 2018), was identified and critically appraised using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Higgins *et al.* 2011), Appendix B1, and summarised in Table 6. The intervention arm was specified screening (including three patient pathways) and invitation to nurse-led liver clinic where serum fibrosis markers and transient elastography were measured. Standard care was the comparator. Patient characteristics (age, gender, diabetes and alcohol use) were different between intervention and comparator centres which the authors attributed to one centre having a high population of university students.

However, it is unclear whether new cases of liver fibrosis or cirrhosis identified within this study were a direct result of transient elastography measurement with FibroScan or due to the targeted screening approach, or additional liver function test and serum fibrosis markers. Due to this, only results from the intervention arm are included in this assessment.

Table 6: Cochrane risk of bias for included RCTs

Study	N*	A	B	C	D	E	F	G	Overall quality**
El-Gohary *et al.* 2018	53,074 (n=910 FibroScan)	?	☹	☹†	☹	☺	☹	☹	Low

Key: ☺, low risk of bias, ☹, high risk of bias; ?, unclear risk of bias.
A, random allocation sequence (selection bias); B, allocation concealment (selection bias); C, blinding of participants and personnel (performance bias); D, blinding of outcome assessment (detection bias); E, incomplete outcome bias (attrition bias); F, selective reporting (reporting bias); G, other bias (for example industry involvement in finding, major concerns over generalisability. As domain G is particularly subjective and partly dependent on journal editorial policy, it is not used in overall summary of evidence.
* Total number of patients randomised.
** Overall summary of study quality (consistent with GRADE methodology):
High: Five or six domains A to F at low risk of bias or no high risk of bias in any single domain.
Moderate: high risk of bias in at least two domains (A to F) and low risk of bias in at least three domains (A to F).
Low: high risk of bias in three or more domains (A to F).
† high risk of bias but blinding of intervention not possible

The EAC identified no diagnostic accuracy studies. One cross-sectional study did report on test agreement between M+ and XL+ probes, however authors acknowledged the limitation of their study to assess diagnostic accuracy due to lack of confirmation against histological findings (Harris *et al.* 2018).

Five cross-sectional studies were critically appraised using the STROBE cross-sectional checklist (Harman *et al.* 2018; Harman *et al.* 2015; Harris *et al.* 2019; Harris *et al.* 2018; Surey *et al*. 2019), four of which were prospective studies related to the Nottingham Community Liver Biomarkers study Appendix B2.

Two single-arm observational cohort studies were critically appraised using the STROBE cohort checklist (Reinson *et al.* 2021; Matthews *et al.* 2019), who followed patients for 53 and 6 months respectively, Appendix B3.

The remaining ten studies were only available in abstract form and the EAC did not critically appraise them. However, they have been included in the assessment due to their value in reporting test failure, uptake, NHS resources and morbidity outcomes.

Ten studies recruited patients with suspected alcohol-related liver disease (AFLD), eight suspected hepatitis C virus infection (HCV), five suspected non-alcohol fatty liver disease (NAFLD), with some studies recruiting multiple risk groups. However, there was variation in measurement of alcohol use across studies recruiting patients at risk of alcohol-related liver disease: alcohol AUDIT questionnaire score of 8 or greater (El-Gohary *et al.* 2018), greater than 14 units per week in women and greater than 21 units in men or presence of READ codes related to alcohol misuse (Harman *et al.* 2015), weekly alcohol use greater than 50 units or greater than 100 units (Surey *et al.* 2019) and attendance at alcohol or drug or addiction services (Roberts *et al.* 2015). There was also variation in definition of obesity across studies: BMI greater than or equal to 30 kg/m^2 (Matthews *et al.* 2019) and BMI greater than or equal to 28 kg/m^2 (Harris *et al.* 2018), the latter being a consequence of increased prevalence of people with Asian ethnicity included in the study. However, overlap of risk factors (type 2 diabetes, obesity, hazardous alcohol use, hepatitis) was commonly reported (Harman *et al.* 2015; Harris *et al.* 2018).

5.3 *Results from the evidence base*

The EAC cross-tabulated the 19 included studies against the outcomes listed in the final scope (NICE MT562 Final Scope, 2021), Table 7.

Table 7: Cross-tabulation of included studies against outcomes.

				Subgroup			Outcomes										
Trial name	Author (year)	Study design (no. of patients invited / no. of patients attending and TE attempted)	Setting	Suspected NAFLD (e.g. metabolic syndrome, type 2 diabetes)	Suspected alcohol-related liver disease (e.g. hazardous alcohol use)	Hepatitis	Test accuracy	Test agreement	Test failure	Uptake	Change in behaviour	NHS resource use (incl. referral to secondary care)	Referral to alcohol/weight management services	Severity of liver fibrosis	Device related adverse events	Mortality	Morbidity
LOCATE study	El-Gohary *et al.* (2018)	Cluster RCT feasibility (n=2082 / TE=910)	GP	✓	✓												
	Reinson et al. (2021)	Cohort (n=116 / TE=59)	GP	✓	✓												
Nottingham Community Liver Biomarker Cohort	Harman *et al.* (2018)	Cross sectional (n=2022 / TE=919)	GP	✓	✓												
	Harman *et al.* (2015)	Cross sectional (n=504/ TE=378)	GP	✓	✓		$										
	Harris *et al.* (2019)	Cross sectional (n=1023 / TE=576)	GP	✓	✓												
	Harris *et al.* (2018)	Cross sectional (n=1167 / TE=477ǂ)	GP	✓	✓			&									
	Knight *et al.* (2020)	Qualitative (n=28 / TE=20)	GP	✓	✓												
NR	Surey *et al.* (2019)	Cross sectional (n=461 / TE=295)	Drug and alcohol services, homeless day centres, homeless hostels		✓	✓											
NR	†Hosack *et al.* (2019)	Cross-sectional (n=476 / TE=455)	GP	✓	✓												
NR	†Mohamed *et al.* (2020)	Cross-sectional (n=NR / TE=124)	Pop-up clinics		✓	✓											
NR	†Corrigall *et al.* (2018)	Cohort (n=174 / TE=NR)	Community drug and alcohol centres			✓											
NR	Matthews *et al.* (2019)	Cohort (n=NR / TE=79)	Community alcohol support centre	✓	✓												
Vulnerable Adults Liver Disease (VALID) study	†Hashim *et al.* (2019)	Cohort (n=131 / TE=127)	Homeless hostels		✓	✓											
NR	†McGinley *et al.* (2017)	Cohort: retrospective (n=231 / TE=179)	Addiction and primary care clinic			✓											
ITTREAT study	†O'Sullivan *et al.* (2019)	Cohort (n=573, TE=NR)	Drug and alcohol treatment centre		✓	✓											
NR	†Roberts *et al.* (2015)	Cohort: prospective (n=527 / TE=189)	Community clinic		✓												
NR	†Siu *et al.* (2019)	Cohort (n=53 / TE=49)	GP diabetic clinic	✓			$										
HepCATT study	†Irving *et al.* (2017)	Before-and-after (n=1232 / TE=NR)	Drug treatment centre			✓											
NR	†Montague *et al.* (2020)	Qualitative (n=35 / TE=NA)	Outreach service			✓											

Abbreviations: NA, not applicable; NR, not reported;
†Abstract only
ǂpatients in study assigned to multiple risk groups
[&]probe agreement only
[$]reported accuracy of liver fibrosis scores when compared to outcomes using FibroScan

Test accuracy

The EAC identified no diagnostic accuracy studies.

The abstract by Sui *et al.* (2019) reported that 22 of 49 (45%) patients attending a type 2 diabetes clinic at their GP had clinically significant fibrosis (greater than 7 kPa). However, 12 of 14 (86%) patients who attended a follow-up FibroScan in a hepatology clinic had decreased transient elastography measurements after being given lifestyle modification advice, but the time interval between scans was undefined. The abstract also reported that serum liver fibrosis scores were poor at detecting clinically significant fibrosis as determined by FibroScan as the reference test (AUROC 0.57, 0.52, 0.42 for NAFLD score, APRI score and FIB-4 respectively) but better at detecting advanced fibrosis greater than 12 kPa (AUROC 0.81, 0.76 and 0.73 for NAFLD, APRI and FIB-4 respectively).

Harman *et al.* (2015) did not explicitly report the test accuracy of transient elastography, however did report on the proportion of fibrosis and cirrhosis cases missed, had ALT and serum (APRI, FIB-4) score thresholds been applied without transient elastography as an incidental finding of the study, Table 8.

Table 8: Proportion of fibrosis and cirrhosis cases missed using liver fibrosis scores from Harman *et al.* (2015)

Author (year)	Variable (cut-off)	Elevated liver stiffness missed	Liver fibrosis on biopsy missed	Liver cirrhosis missed
Harman *et al.* (2015)	ALT (>35 U/L for women, >45 U/L for men)	72.4%	60%	90.9%
	ALT (>19 U/L for women, >30 U/L for men)	41.8%	NR	18.2%
	APRI (>1.5)	NR	NR	100%
	FIB-4 (>3.25)	NR	NR	81.8%
Abbreviations: ALT, serum alanine aminotransferase levels; APRI, AST to platelet ratio index; NR not reported				

Matthews *et al.* (2019) also reported that of the 12 participants with a transient elastography greater than or equal to 8.0 kPa who were referred to a nurse-

led clinic and subsequent onward referral to specialist liver services (including ultrasound/CT/MRI), 6 were diagnosed with definite liver cirrhosis and 4 were diagnosed with fibrosis.

A definitive trial to assess the diagnostic accuracy of people indicated for FibroScan in primary care compared with liver biopsy (as a reference standard in the detection of liver fibrosis) is likely to be unethical. One clinical expert noted the study by Thiele *et al.* (2018) which included 269 patients with a reliable transient elastography measurement taken in a secondary care setting (threshold of 15 kPa and above) compared FibroScan with liver biopsy as a reference standard for those who went on to have liver biopsy. Of the 517 eligible, 289 had a biopsy, and 112/228 exclusions were because of a declined biopsy, therefore risk of spectrum bias. The study reported per protocol sensitivity and specificity of 91% [81% to 97%] and 95% [91% to 98%] respectively.

Test agreement

No study reported on test agreement between FibroScan measurement in a primary or community care setting and FibroScan measurement in a secondary or specialist care setting.

Harris *et al.* (2018) did however report on liver stiffness measurement between probes in an obese population. Linear regression analysis confirmed that liver stiffness (in kPa) was correlated between XL+ and M+ probes (R^2=0.78, p<0.001). Bland-Altman analysis demonstrated a difference in liver stiffness between probes, which was statistically significant; mean bias 0.82 (95% CI 0.58 to 1.08) kPa with the 95% limits of agreement (the upper and lower values between which 95% of paired comparisons lie) between -4.14 and +5.79 kPa. The study also reported that 5.2% of patients who were deemed to have clinically significant liver disease using the M+ probe, were restratified to normal liver stiffness when using the XL+ probe. Risk of re-stratification was univariately associated with BMI, type 2 diabetes, hypertension and hypercholesterolaemia), and multi-variately with BMI, when adjusting for age, gender and ethnicity.

There is no published direct head-to-head comparison of different models of FibroScan; equivalence is therefore assumed through valid CE certification, for which the Company presented evidence of equivalence for scrutiny by a Notified Body for all currently available models.

Test failure

Test failure was consistently defined across five studies, as the inability to obtain ten valid measurements with the FibroScan device (which is in line with FibroScan instructions for use). Test failures for the majority of studies were low (1.7% to 2.2%), Table 9. Higher failure proportions were reported by Harris *et al.* (2018) (33.8% failures using M+ probe, 9.9% using XL+ probe) however this focused on an obese subgroup of the Nottingham cohort study. Matthews *et al.* (2019) reported that valid measurements were not possible in three patients, all of whom had a BMI greater than 30 kg/m^2. Reinson *et al.* (2021) also reported that only one patient was unable to be scanned due to BMI greater than 50 kg/m^2. The clinical experts advised that test failure is high during the learning curve (EAC Correspondence Log, 2021).

Table 9: Summary of test failures

Author (year)	Failure proportion; failures/total patients (%)
Reinson *et al*. (2021)	1/60 (1.7%)ǂ
El-Gohary *et al*. (2018)	NR (1.9%)
Harman *et al*. (2018)	20/919 (2.2%)
Harris *et al*. (2018) - M+ probe - XL+ probe	 161/477 (33.8%) 47/477 (9.9%)
Matthews *et al*. (2019)	3/79 (3.8%)
Abbreviations: NR not reported; ǂFailure proportion of rescan	

However, different definitions of test unreliability were used across three studies, Table 10. Harris *et al.* (2018) reported increased reliability in an obese cohort when using the XL+ probe (98.5% vs. 77.4%, p=0.028), and that only 0.8% (4 of 477) of patients did not obtain a reliable reading using either probe.

Table 10: Summary of test unreliability

Study (year)	Definition of unreliable	Definition of reliable	Unreliable acquisitions n patients (%)
Harris *et al*. (2019) a) M+ probe b) XL+ probe	Fewer than 10 valid measurements and IQR/median>0.3	NR	All: 43/576 (7.5%) a) 26/448 (5.8%) b) 17/128 (13.3%)
Harman *et al*. (2018)	Liver stiffness of at least 7.1 kPa and IQR/median>0.3	NR	44/899 (4.9%)
Harris *et al*. (2018) a) M+ probe b) XL+ probe	NR	Minimum of 10 valid measurements, and IQR/median less than 0.3 if measurement greater than 7.1 kPa	a) 165/477 (34.6%) b) 52/477 (10.9%)
	NR	- IQR/median≤0.1; or - IQR/median≤0.3 and >0.1; or - IQR/median>0.3 and measurement <7.1 kPa	a) 108/477 (22.6%) b) 7/477 (1.5%)
Abbreviations: NR not reported; IQR interquartile range			

Uptake

Three studies (El-Gohary *et al.* 2018; Harris *et al.* 2019; Harman *et al.* 2018) identified eligible cohorts from electronic records, and subsequently reported uptake as the proportion of patients who were invited to and attended an additional clinic or GP appointment where FibroScan was conducted. Four additional conference abstracts explicitly reported uptake, Table 11. Reported uptake ranged between 36% (patients attending community clinic; Roberts *et al*. 2015) to 97% (individuals attending homeless hostel; Hashim *et al.* 2019), does not represent the uptake of FibroScan directly, but the uptake of an additional healthcare visit including FibroScan (and additional serum collection in the case of El-Gohary *et al.* 2018). The clinical experts advised that the "did not attend" (DNA) rate is lower for FibroScan in primary care (10%) when compared with FibroScan conducted in a hospital setting (40%); which is in broad agreement with the published literature (EAC Correspondence Log, 2021). The experts also advised that higher attendance rates are observed following abnormal blood test results when compared with routine screening appointments.

Table 11: Summary of attendance at liver assessment appointment.

Study (year)	Setting	Attended clinic n (%)
El-Gohary *et al.* (2018)	GP	All: 910/2082 (43.7%) GP referral: 272/627 (43.4%*) Risk group: 465/1235 (37.7%*) Excess alcohol: 173/220 (78.6%*)
Harris *et al.* (2019)	GP	576/1023 (56.3%*)
Harman *et al.* (2018)	GP	919/2022 (45.5%)
†Hosack et al. (2019)	GP	455/476 (95.6%)
†Hashim *et al.* (2019)	Homeless hotels	127/131 (97%)
†McGinley *et al.* (2017)	Addiction and primary care clinic	179/231 (77%)
†Roberts *et al.* (2015)	Community clinic	189/527 (35.9%*)
*percentage calculated by EAC		

The qualitative study of 20 patients by Knight *et al.* (2020) reported that the invitation to attend an additional transient elastography appointment was unexpected in some patients (such as patients with hazardous alcohol use who were not routinely part of a medical programme) and resulted in anxiety. The study reported that patients with type 2 diabetes were more likely to attend, due to their regular involvement in other screening (such as retinal screening) as part of their routine diabetes care. Many participants (number not defined in the study) reported that transient elastography in their GP practice was more convenient than in a hospital setting, and would result in increased uptake. All participants were willing to undergo further chronic liver disease screening in primary care and reported an interval of three to five years as acceptable for repeated transient elastography scans. A survey of patient acceptability of a hepatitis C virus mobile outreach service reported by Montague *et al.* (2020) found that the majority of comments describing the benefit of not having to attend hospital appointments and a preference for engaging with a peer. O'Sullivan *et al.* (2019) reported that uptake of dried blood spot testing and transient elastography measurement was greater than 97% of individuals attending a drug and alcohol treatment centre as part of an integrated community based hepatitis C service. The abstract by Irving *et al.* (2017) reported that 45 of 569 people (7.9%) attending a drug treatment centre in the intervention period were engaged (had completed investigations

with FibroScan, serum markers, viral load/genotyping and health consultation) compared with 10 of 663 (1.5%) in the baseline period.

Reinson *et al.* (2021) was the only study to report uptake of follow-up clinic appointments where patients were invited to be rescanned using FibroScan after a mean of 54 months from the initial FibroScan measurement. Of the 116 patients who had a baseline measurement greater than or equal to 6.0 kPa and less than 12.0 kPa and were invited for a rescan, 59 participated (50.9%).

Change in behaviour

The cohort study by Reinson *et al.* (2021) which followed patients for an average of 54 months from baseline liver assessment, reported that BMI was statistically lower at follow-up when compared to baseline: 28.1 [24.8 to 33.1] compared to 28.0 [IQR 25.1 to 33.6] kg/m^2 respectively in paired analysis, $p<0.008$. However the clinical significance of this reduction in BMI is unclear given the mean (SD) weight loss of 1.2 (8.4) kg in this patient group after 54 months. Additionally, alcohol AUDIT grade was significantly different at follow-up ($p<0.001$), with a higher proportion of patients reporting hazardous, harmful and dependent grades at follow-up when compared to baseline in unpaired analysis. The authors summarise that there was no substantial impact on weight or alcohol consumption after 54 months follow-up, and that further support is required for patients to make positive and sustained lifestyle changes.

The cohort study by Matthews *et al.* (2019) reported that of 20 patients referred to a nurse clinic with transient elastography greater than or equal to 7.1 kPa, 1 was discharged back to GP due to a period of alcohol reduction over 6 month follow-up.

The qualitative study including 20 participants of a chronic liver disease screening in a primary care setting by Knight *et al.* (2020) reported that both patients with normal and patients with elevated liver stiffness reported contemplation of lifestyle changes.

Roberts *et al.* 2015 stated that 64 patients (33.8%) reported alcohol abstinence since the referral to a community clinic from alcohol or drug service or GP screening using the alcohol AUDIT questionnaire.

McGinley *et al.* (2017) stated that two patients from their cohort of patients recruited from addiction and primary care clinics had relapsed, however no additional context or detail was provided.

NHS resource use (including referral to secondary care)

Five studies explicitly reported on the use of transient elastography (when used as part of a diagnostic algorithm) for consideration of referral to secondary care.
Matthews *et al.* (2019) reported the use of FibroScan as a referral pathway based on their transient elastography results:

- Results less than or equal to 7.0 kPa had lifestyle advice reinforced. 56 of 76 (74%) patients required no onward referral for further investigations;
- Results greater than or equal to 7.1 kPa were offered appointment at NHS nurse-led clinic within same community service on another day, with bloods taken (full liver profile and platelets). A total of 19 of 20 (95%) patients attended;
- Blood results of those between 7.1 kPa and 8.0 kPa were discussed with a consultant hepatologist in order to determine whether further investigations and medical assessment were required. None of the eight patients with transient elastography results in this range required onward referral for medical assessment;
- Of the remaining 12 patients, 7 (9%) had transient elastography reading greater than or equal to 8.0 kPa and less than 12.5 kPa indicating possible significant fibrosis, and 5 (7%) had readings greater than or equal to 12.5 kPa indicating possible cirrhosis. All 12 patients with greater than or equal to 8.0 kPa were referred for ultrasound or CT or MRI, and all attended (100%). The 12 patients

were also referred to specialist liver services for clinical evaluation by consultant hepatologist, where 11 (92%) attended.

Of the 20 participants requiring referral to the nurse-led clinic, 6 were diagnosed with definite liver cirrhosis, 4 were diagnosed with fibrosis and remained within specialist services, 1 was discharged back to GP, 1 did not engage and therefore did not receive a diagnosis. Nine of ten (90%) patients attended six month follow-up appointment.

The abstract by Mohamed *et al.* (2020) reported that 13 of 124 (10.5%) of homeless people undergoing a liver health assessment with FibroScan and hepatitis C virus antibody testing required further management within local hepatology services, with 8 patients testing positive for hepatitis C virus antibodies, 3 with advanced fibrosis (secondary to alcoholic liver disease (ALD)) and 2 with cirrhosis (secondary to NAFLD).

The abstract by Hosack *et al.* (2019) reporting a prospective study of high risk patients in 4 GP practices, reported that 85 of 455 (19%) patients undergoing transient elastography had measurements greater than 10 kPa prompting a referral to secondary care, with 72 of 85 (85%) patients being seen in a hepatology clinic for further assessment and management.

The abstract by Irving *et al.* (2017) reported that referrals from drug treatment centres to hepatology increased from 4.4% (29 of 663) during the baseline period to 14.9% (85 of 569) during the intervention period (intervention including FibroScan, serum fibrosis markers, viral load/genotyping, consultation regarding treatment options).

The abstract by Roberts *et al.* (2015) reported that 17 of 189 (9.0%) individuals within a proactive assessment of liver health in the community were referred to hepatology: 7 due to transient elastography measurements greater than 20 kPa and 10 due to clinical grounds.

A small number stated the need for referral to secondary care due to an inability to obtain transient elastography measurements using FibroScan in primary care. Knight *et al.* (2020) reported that it was not possible to obtain a valid liver assessment in the community in one patient (5%), who was

subsequently referred to secondary care for transient elastography assessment. Furthermore, the Nottingham cohort study (Harman *et al.* 2018, 2015) reported that patients with a BMI greater than 35 kg/m^2 or who failed initial measurement underwent transient elastography in a hospital setting with an XL+ probe. However it is not reported why the XL+ probe was not used in the primary or community care setting, therefore the EAC assumes this is related to availability at the time of the study.

None of the studies reporting on NHS resource usage were included in the Company economic model.

Referral to alcohol/weight management services

No study reported on referral to alcohol or weight management services.

Severity of liver fibrosis

The majority of studies (17 of 19, 89%) reported the severity of liver fibrosis at the time of testing Table 12a. Only 2 identified studies reported long-term fibrosis outcomes at 6 months (Matthews *et al.* 2019) and 54 months (Reinson *et al.* 2019). The EAC notes that the two abstracts that did not report severity of liver fibrosis were primarily focused on Hepatitis C viral infection.

Elevated liver stiffness was consistently reported as transient elastography measurements of 8 kPa and above, and ranged between 9.8% (El-Gohary *et al.* 2018: in 173 patients within the hazardous alcohol use subgroup recruited in a GP setting) and 27% (McGinley *et al.* 2017: in 179 patients recruited from addiction and primary care clinics).

Probable cirrhosis was broadly defined as transient elastography measurements of 13 kPa or above, with a threshold of 12.5 kPa applied in a single study (Matthews *et al.* 2019). This ranged between 2.3% (El-Gohary *et al.* 2018: in 173 patients within hazardous alcohol use subgroup recruited in a GP setting) and 17% (Hashim *et al*. 2019: 127 patients recruited from

homeless hostels). However the EAC notes that the clinical experts stated a higher established threshold for cirrhosis of 15 kPa.

The method of confirmation of liver fibrosis/cirrhosis was variable across studies. In the study by El-Gohary *et al.* (2018), all diagnoses were reviewed by a GP and consultant hepatologist, however additional tests were not reported in the study. Harris *et al.* (2019) reported elevated liver stiffness in 12.4% of patients identified from an electronic patient search who subsequently attended a transient elastography appointment. A total of 56 (84.8%) were reviewed by a hepatologist in the community, of which 12 (18.2%) were diagnosed with cirrhosis based on combination of transient elastography, clinical acumen, radiology and endoscopy criteria. Harman *et al.* (2015) reported that of the 98 patients with elevated liver stiffness referred for community assessment by a hepatologist, liver biopsy was performed in 25 patients where there was diagnostic uncertainty on review of clinical and TE information (25.5%). Liver fibrosis was confirmed in 20 patients, and steatohepatitis in 5 patients. Overall 11 patients were newly diagnosed with liver cirrhosis during study period based on clinical, radiological and/or histology assessments; 4 of which had additional evidence of portal hypertension. The abstract by Hosack *et al.* (2020) reported that of the 72 of 85 patients referred to secondary care based on transient elastography results greater than 10 kPa and attending a hepatology clinic: 5 had thrombocytopenia, 13 had splenomegaly sonographically, 28 underwent gastroscopy for variceal surveillance of which 3 had portal hypertensive gastropathy, and 3 had gastro-oesophageal varices. A total of 13 new diagnoses of cirrhosis were detected (although the transient elastography of these patients is unclear): 1 with chronic hepatitis C, 1 with autoimmune hepatitis, and 1 with a neuroendocrine tumour.

Only 1 conference abstract (Mohamed *et al.* 2020) reported on CAP, with an average across 124 participants of 240; however the interpretation of this and its influence on diagnosis was not reported.

Table 12a: Studies reporting on severity of liver fibrosis.

Study (year)	Subgroup	Category of liver disease (thresholds)	n (%)
†Corrigall *et al.* (2018)	All (n=174)	Cirrhosis (undefined)	21 (12%)
El-Gohary *et al*. (2018)	All (n=26,838)	With READ code for liver disease	*287 (1.1%)
	All (n=26,838)	With READ code for liver disease or nurse-led clinic (intervention arm: TE, HA, P3NP, platelet count)	544 (2.0%)
	Pathway 1: GP referral (n=271)	No fibrosis (<6 kPa) Liver warning (6-8 kPa) Progressive fibrosis (8-12.9 kPa) Probable cirrhosis (≥13 kPa)	135 (49.8%) 70 (25.8%) 52 (19.2%) 14 (5.2%)
	Pathway 2: risk factors (n=466)	No fibrosis (<6 kPa) Liver warning (6-8 kPa) Progressive fibrosis (8-12.9 kPa) Probable cirrhosis (≥13 kPa)	248 (52.1%) 116 (24.8%) 76 (17.4%) 26 (5.8%)
	Pathway 3: hazardous alcohol use (n=173)	No fibrosis (<6 kPa) Liver warning (6-8 kPa) Progressive fibrosis (8-12.9 kPa) Probable cirrhosis (≥13 kPa)	122 (70.5%) 34 (19.7%) 13 (7.5%) 4 (2.3%)
Harris *et al.* (2019)	All (n=533)	Elevated liver stiffness (≥8 kPa)	66 (12.4%)
Harman *et al.* (2018)	All (n=899)	Elevated liver stiffness (≥8 kPa) - Hazardous alcohol - Type 2 diabetes - Hazardous alcohol and type 2 diabetes - Elevated ALT levels	230 (25.6%) - 19.2% - 31.5% - 37.5% - 45.3%
		Fibrosis (undefined)	203 (22.1%)
		Cirrhosis (undefined) - Hazardous alcohol - Type 2 diabetes - Hazardous alcohol and type 2 diabetes - Elevated ALT levels	27 (3.0%) - 2.8% - 3.7% - 7.7% - 5.6%
†Hashim *et al.* (2019)	All (n=127)	Clinically significant fibrosis (≥8 kPa) Cirrhosis (≥13 kPa)	33 (26%) 21 (17%)
Matthews *et al.* (2019)	All (n=76)	Warning (≥7.1 & <8 kPa) Significant fibrosis (≥8 & <12.5 kPa Probable cirrhosis (≥12.5 kPa)	8 (10.5%) 7 (9.2%) 5 (6.6%)
†McGinley *et al.* (2017)	All (n=179)	F3 fibrosis or higher (undefined)	48 (27%)
†O'Sullivan *et al.* (2019)	Positive hepatitis C PCR (n=259)	F2 fibrosis or higher (undefined)	NR (47%)
†Roberts *et al.* (2015)	All (n=182 with results available)	< 8kPa 8-12 kPa 12-20 kPa >20kPa	146 19 10 7
Surey *et al.* (2019)	All (n=295)	F1 (undefined) F2 (undefined) F3 (undefined) F4 (undefined)	184 (62.4%) 44 (14.9%) 22 (7.5%) 45 (15.3%)
Abbreviations: ALT; HA; P3NP; TE transient elastography; *in patients aged over 25 years †Abstract ‡subset of Harman *et al.* 2018 study.			

Reinson *et al.* (2021) followed 59 patients at a mean follow-up of 54 months following a first liver fibrosis assessment in primary care. The severity of liver fibrosis at follow-up was reported using 2 sets of thresholds (original LOCATE study thresholds and validated thresholds published subsequently; stage only reported in 58 patients), Table 12b. The study also reported progression (significant or advanced change) of liver fibrosis stage in 19% (11 of 59 patients) over the 54 months follow-up, Table 12c.

Table 12b: Severity of liver fibrosis in 58 patients after 54 months follow-up using different thresholds (Reinson *et al.* 2021)

Threshold from LOCATE study	n (%)	Threshold	n (%)
No fibrosis	27 (45.8%)	F0 (<6.0 kPa)	26 (44.8%)
Liver warning	14 (23.7%)	F1 (6.0-8.1 kPa)	16 (27.6%)
Progressive fibrosis	10 (16.9%)	F2 (8.2-9.6 kPa)	6 (10.3%)
		F3 (9.7-13.5 kPa)	3 (5.2%)
Presumed cirrhosis	7 (11.9%)	F4 (≥13.6 kPa)	7 (12.1%)

Table 12c: Change in stage of liver fibrosis in 59 patients during follow-up (Reinson *et al.* 2021)

Change in liver fibrosis stage	n (%)
No change	19 (32.2%)
Decrease	29 (49.1%)
Significant change (F1 to F2)	2 (3.4%)
Advanced change (F1/F2/F3 to F3/F4)	9 (15.3%)
F1: 6.0-8.1 kPa F2: 8.2-9.6 kPa F3: 9.7-13.5 kPa F4: ≥13.6 kPa	

Device-related adverse events

No study reported on device-related adverse events.

Mortality

No study reported on mortality

Morbidity

Two studies compared demographics of patients with and without elevated transient elastography measurements, Table 13a.

Three studies conducted univariate analysis to determine predictors of elevated transient elastography (greater than or equal to 8.0 kPa). Univariate logistic regression by Harris *et al.* (2019) identified that increasing BMI, age, diagnosis of type 2 diabetes, hypertension, and hyperlipidaemia were significantly associated with elevated transient elastography, Table 13b. Multivariate logistic regression by Harris *et al.* (2019) confirmed that increased BMI (OR 1.17 [1.11 to 1.24] for a unit increase in BMI, kg/m^2) and presence of type 2 diabetes (OR 3.14 [1.67 to 5.91]) were associated with elevated transient elastography outcome when accounting for age and gender. However, it is unclear to the EAC why some covariates deemed significant in univariate analysis were not included in multivariate analysis.

Harman *et al.* (2018) reported that univariately age, BMI (continuous variable), hazardous alcohol use (binary), current alcohol units, type 2 diabetes, raised ALR, obesity, ischaemic heart disease, hypertension, hyperlipidaemia, metabolic syndrome were significantly associated with elevated transient elastography. Similarly, Hashim *et al.* (2019) reported that positive hepatitis C virus infection, and alcohol AUDIT score above 20 were independent predictors of elevated transient elastography. However, there is no evidence to suggest that either study accounted for multiple statistical testing.

Binary logistic regression by Reinson *et al.* (2021) found that age, sex, diagnosis of type 2 diabetes, baseline transient elastography, baseline BMI and alcohol AUDIT grade were not predictors of progression of liver fibrosis (to F3 or F4), or regression or no change (F0 to F2) in 59 patients after 54 months follow-up, Table 13c. However, the authors acknowledge that their study was not powered to detect this outcome.

Table 13a: The proportion of patients with normal and elevated liver stiffness by comorbidity (univariate analysis)

Study (year)	Subgroup	Variable	Normal liver stiffness	Elevated liver stiffnessł	p-value
Harris *et al.* (2019)	All	Mean age (SD)	57.7 (14.0)	62.3 (12.2)	0.012*
		Obesity	283 (60.6%)	52 (78.8%)	0.004*
		Type 2 diabetes	128 (27.4%)	35 (53.0%)	<0.001*
		Hazardous alcohol use	141 (30.2%)	14 (21.2%)	0.133
		Hypertension	187 (40.0%)	44 (66.7%)	<0.001*
		Hyperlipidaemia	192 (41.1%)	41 (62.1%)	0.001*
		BMI			<0.001*
		< 25	85 (18.3%)	4 (6.1%)	
		25-29.9	136 (29.3%)	10 (15.2%)	
		30-34.9	173 (37.2%)	27 (40.9%)	
		≥35.0	71 (15.3%)	25 (37.9%)	
		Ischaemic heart disease	35 (7.5%)	9 (13.6%)	0.096
		Median ALT (IQR), U/L	24 (18 to 34)	32 (25 to 47)	<0.001*
		ALT ≥45, U/L	53 (12.1%)	18 (27.3%)	0.001*
		Median platelets (IQR), 10^9/L	249 (209 to 292)	240 (199 to 305)	0.719
Harman *et al.* (2018)	All (n=669 normal, n=230 elevated)	Median age (IQR)	60.0 (48.0 to 69.0)	63.0 (52.0 to 70.0)	0.02*
		Median BMI (IQR)	27.4 (24.2 to 30.9)	31.6 (28.2 to 35.3)	<0.001*
		Hazardous alcohol use	316 (47.3%)	75 (32.6%)	<0.001*
		Type 2 diabetes	371 (55.5%)	171 (74.4%)	<0.001*
		Raised ALT	87 (13.0%)	73 (31.7%)	<0.001*
		Obesity	210 (31.8%)	140 (60.9%)	<0.001*
		Ischaemic heart disease	69 (10.3%)	38 (16.5%)	0.01*
		Hypertension	269 (40.3%)	126 (54.8%)	<0.001*
		Hyperlipidaemia	433 (64.8%)	176 (76.5%)	<0.001*
		Metabolic syndrome	170 (25.5%)	118 (51.3%)	<0.001*
	Hazardous alcohol use (n=316 normal, n=75 elevated)	Obesity	63 (20.3%)	33 (44.0%)	<0.001*
		Median BMI (IQR)	25.7 (22.8 to 28.7)	28.7 (26.5 to 33.3)	<0.001*
		Metabolic syndrome	28 (8.9%)	20 (26.7%)	<0.001*
		Raised ALT	42 (13.3%)	25 (33.3%)	<0.001*

	Type 2 diabetes (n=371 normal, n=171 elevated)	Obesity BMI Metabolic syndrome Raised ALT	157 (42.6%) 28.90 (25.90 to 32.00) 157 (42.3%) 28 (7.6%)	116 (67.8%) 32.45 (29.00 to 36.30) 109 (63.7%) 46 (26.9%)	<0.001* <0.001* <0.001* <0.001*
Abbreviations: ALT, alanine transaminase; BMI, body mass index; IQR, interquartile range; SD, standard deviation ł defined as greater than 8.0 kPa * result is statistically significant					

Table 13b: Elevated liver stiffness or cirrhosis (univariate analysis).

Study (year)	Subgroup	Comorbidity	Odds ratio (of elevated liver stiffness, that is 8.0 kPa or higher, with and without comorbidity) [95% CI]	Odds ratio (of cirrhosis, with undefined threshold, with and without comorbidity) [95% CI]
Harris *et al.* (2019)	All patients (n=533)	BMI	1.12 [1.08 to 1.18]*	NR
		Age	1.02 [1.00 to 1.04]*	NR
		Gender	1.26 [0.75 to 2.12]	NR
		Type 2 diabetes	2.99 [1.77 to 5.05]*	NR
		Hazardous alcohol use	0.62 [0.33 to 1.16]	NR
		Hypertension	2.99 [1.74 to 5.16]*	NR
		Hyperlipidaemia	2.35 [1.38 to 3.99]*	NR
		Ischaemic heart disease	0.75 [0.48 to 1.18]	NR
		Previous smoker	1.56 [0.91 to 2.68]	NR
Harman *et al.* (2018)	Hazardous alcohol users (n=391)	Obesity	3.1 [1.8 to 5.3]*	5.6 [1.6 to 19.7]*
		Metabolic syndrome	3.7 [2.0 to 7.1]*	2.8 [0.7 to 10.9]
		Raised ALT	3.3 [1.8 to 5.8]*	2.9 [0.8 to 10.1]
	Type 2 diabetes (n=543)	Obesity	2.9 [1.9 to 4.2]*	9.4 [2.2 to 40.9]*
		Metabolic syndrome	2.4 [1.6 to 3.5]*	4.4 [1.4 to 13.2]*
		Raised ALT	4.5 [2.7 to 7.5]*	2.2 [0.8 to 6.2]
	Hazardous alcohol users & type 2 diabetes (n=64)	Obesity	2.1 [0.8 to 5.9]	5.1 [0.5 to 48.2]
		Metabolic syndrome	1.7 [0.6 to 4.6]	2.2 [0.3 to 14.1]
		Raised ALT	3.0 [0.8 to 12.0]	1.4 [0.1 to 13.9]
†Hashim *et al.* (2019)	All	Positive hepatitis C RNA	1.90 [1.20 to 3.00]*	NR
		Alcohol AUDIT score>20	5.53 [2.13 to 14.33]*	NR

Abbreviations: ALT, Alanine transaminase; AUDIT, alcohol use disorders identification test; BMI, body mass index; CI, confidence interval; NR, not reported
*statistically significant
†available as abstract only

Table 13c: Predictors of liver fibrosis progression or regression/no change

Study (year)	Subgroup	Baseline	Odds ratio of liver fibrosis progression [95% CI]	Odds ratio of liver fibrosis regression/no change [95% CI]
Reinson *et al.* (2021)	All patients (n=59)	Type 2 diabetes	1.909 [0.354 to 10.297]	1.597 [0.319 to 8.005]
		Age (years)	1.019 [0.948 to 1.096]	0.983 [0.917 to 1.053]
		Gender (female)	0.998 [0.191 to 5.213]	0.826 [0.171 to 3.996]
		Baseline TE reading (kPa)	1.012 [0.620 to 1.652]	1.061 [0.648 to 1.735]
		Baseline BMI (kg/m^2)	1.027 [0.921 to 1.145]	0.999 [0.898 to 1.111]
		Alcohol AUDIT grade (high)	0.838 [0.130 to 5.412]	0.564 [0.094 to 3.400]

Abbreviations: ALT, alanine transaminase; AUDIT, alcohol use disorders identification test; BMI, body mass index; CI, confidence interval; TE, transient elastography
*statistically significant

6 Adverse events

The Company reported in its submission to have searched the Manufacturer and User Facility Device Experience (MAUDE) database, of the US Food and Drug Administration (FDA). This search for the brand name “Fibroscan” was done in January 2020, with no date restrictions, and returned no results. The EAC repeated this search and added the manufacturer “Echosens” on 22 September 2021, and also found no results. The EAC also searched for any alerts, recalls or safety information published by the Medicines and Healthcare products Regulatory Agency (MHRA) on 22 September 2021 relating to “Fibroscan” or “Echosens”, and confirms that no results were identified.

The EAC broadened the inclusion criteria of its independent literature search to include any study design, which reported the use of FibroScan outside of a hospital setting. Five studies reported on test failure and three reported test unreliability of FibroScan in primary/community care setting (see Section 5, Table 9 and Table 10 respectively). However, the EAC found no reported adverse events causing patient harm in the published literature.

Adverse events identified by the clinical experts (EAC Correspondence Log, 2021) included:

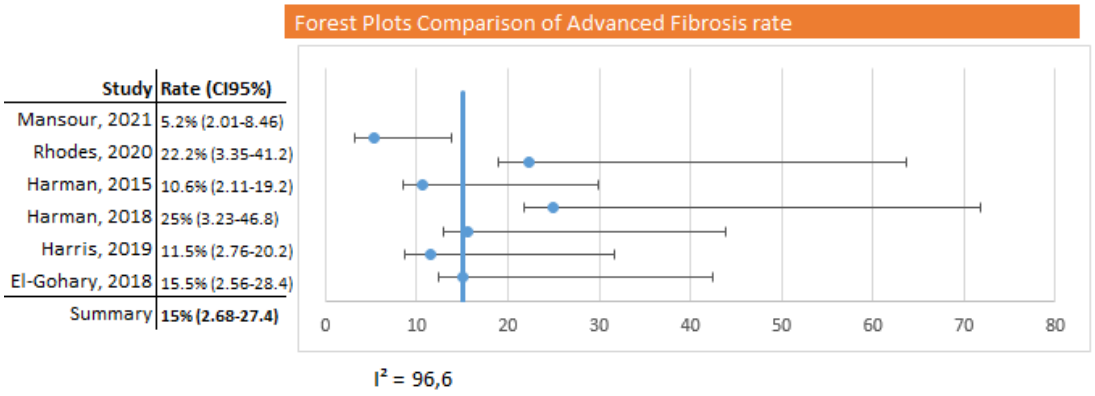
- infrequent and minimal bruising at ribs (however the EAC would consider this a consequence of user technique not specific to the device),
- false negative results from FibroScan potentially giving false reassurance that lifestyle is appropriate to the patient
- adverse mental health from incorrect diagnosis of cirrhosis (false positive).

The EAC is satisfied that there are no major safety concerns for the Fibroscan device.

7 Evidence synthesis and meta-analysis

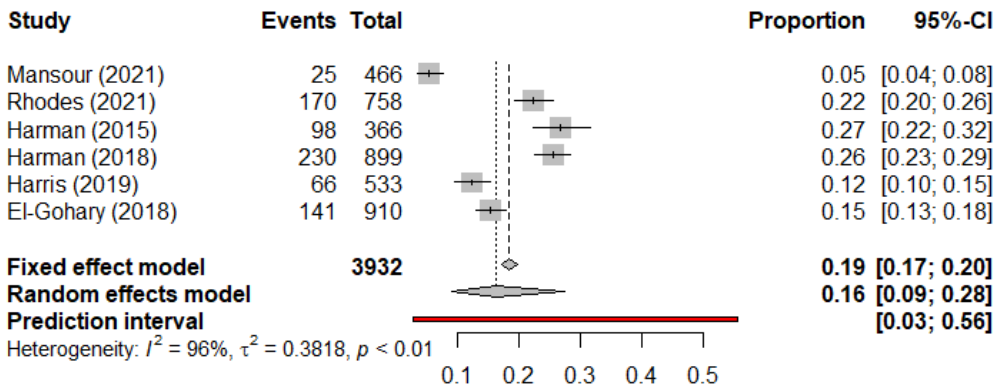
The Company conducted meta-analysis combining the detection rate of advanced fibrosis reported by 6 studies (Mansour *et al.* 2021; Rhodes *et al.* 2021; Harris *et al.* 2019; El-Gohary *et al.* 2018; Harman *et al.* 2018; Harman *et al.* 2015) and reported a diagnosis rate of 15% [95% CI 2.7% to 27.4%], Figure 2. The Company referenced a step-by-step guide to conducting meta-analysis and forest plots using Microsoft Excel spreadsheet (Neyeloff *et al.* 2012).

Figure 2: Company meta-analysis in Excel [taken from the Company clinical evidence submission]



It is unclear to the EAC why the Company have used meta-analysis to combine the proportion of patients with liver fibrosis (as identified by FibroScan and other clinical indicators) across multiple studies conducted in different populations and different settings. The EAC attempted to numerically replicate the meta-analysis in R (version 4.0.2) (R Core Team, 2020) using the *meta* package (version 4.16-2) (Balduzzi *et al.* 2019). However, the EAC was unable to calculate the same proportion of events for Harman *et al.* (2015) and Harris *et al.* (2019), and the confidence intervals throughout meta-analysis did not align with the Company's analysis, see Figure 3.

Figure 3: EAC attempt to replicate the Company meta-analysis in R.



The EAC recommends that three of the six studies included in the Company meta-analysis should be omitted. The EAC previously excluded two of the studies due to secondary care setting of the transient elastography measurement (Mansour *et al.* 2021; Rhodes *et al.* 2021); see Section 4.2. Three of the studies included in the Company's meta-analysis were from the Nottingham Community Liver Biomarkers Cohort study, with direct overlap in patient recruitment dates between Harman *et al.* (2018) and Harman *et al.* (2015, duplication of results). Diagnosis of advanced fibrosis across studies used different combinations of FibroScan, clinical data, liver aetiology blood tests, further imaging (radiology, ultrasound, endoscopy) and liver biopsy. Furthermore, different thresholds were applied to FibroScan results to define advanced fibrosis:

c) Mansour *et al.* (2021) used greater than 8 kPa;

d) Harman *et al.* (2018), Harman *et al.* (2015) and Harris *et al.* (2019) used greater than or equal to8 kPa;

e) Rhodes *et al.* (2021) used greater than or equal to 11 kPa for alcohol-related liver disease and greater than or equal to 10 kPa for non-alcoholic fatty liver disease;

f) El-Gohary *et al.* (2018) used between 8 and 12.9 kPa.

The Company correctly highlight significant statistical heterogeneity in the meta-analysis (I^2 between 75 and 100%), as illustrated by the forest plot in Figure 3. However, the EAC would consider that the study heterogeneity is so

great (variation in study population, intervention applied, thresholds applied and definition of outcome) that meta-analysis is not appropriate.

8 Interpretation of the clinical evidence

Due to the inclusion criteria applied by the EAC, the published studies included within this assessment report were all conducted in a UK setting, and therefore considered generalisable to the NHS. There are no major safety concerns regarding FibroScan.

The EAC has examined the claimed benefits of FibroScan made by the Company in the context of the clinical evidence included, Table 14.

Table 14: Summary of clinical evidence for claimed benefits

	Claimed benefits	EAC opinion
Patient benefit	Enables earlier or more accurate diagnosis	Earlier diagnosis of fibrosis: Benefit likely Driven by more people attending appointments involving FibroScan measurement in primary/community care setting compared with secondary/specialist care setting. More accurate diagnosis of fibrosis: Cannot be proved Conducting histology on all patients would be unethical or have high dropout rates, no comparative studies identified.
	Enables a test, procedure or treatment to be done non-invasively	Benefit not proved There is no direct comparative evidence to suggest use of FibroScan in primary/community care reduces the need for liver biopsy. There is potential to use FibroScan in primary/community setting as a triage for secondary care referral. Clinical experts have advised that transient elastography outcome can guide frequency of liver assessment. However, the outcome of transient elastography conducted in primary/community care setting is unlikely to be different to the outcome of transient elastography conducted in a secondary/specialist setting if using the same model of FibroScan on the same at risk patient population.
	Reduces risks, side effects or complications	Benefit not proved There is no direct comparative evidence to suggest use of FibroScan in primary/community care setting reduces the need for liver biopsy (as above). No adverse events associated with FibroScan were identified in the

		literature; this would be applicable to FibroScan conducted in any setting. The experts agreed that the lifestyle interventions that would be recommended if a patient received a false positive result (to support weight loss or reduce drinking) are not harmful (in fact, likely to be beneficial in any case for patients at risk of fibrosis) so no danger of harm caused through inappropriate treatment. Avoidable biopsy may be a consequence of a false positive; however other investigations are likely to be carried out in secondary care before proceeding to liver biopsy (EAC Correspondence Log, 2021). The clinical experts also considered the possibility that false negative tests may provide false reassurance and encourage persisting with negative behaviour. However disease progression tends to be slow, and at risk patients are reviewed regularly therefore the implications of this are minimal (EAC Correspondence Log, 2021).
	Enable behaviour changes or lifestyle interventions	Benefit likely It is plausible that increased attendance of liver assessment (including FibroScan) in a primary/community setting increases the proportion of patients and frequency at which patients receive behavioural/lifestyle advice. Reinson *et al.* (2021) suggests that alcohol and weight advice were not adhered to at 54 months follow-up following first liver assessment, which suggests additional support or more frequent measurement may be required in some at-risk patient groups.
System benefits	Enables delivery of care in primary care setting (for example, GP or community services) rather than in secondary care setting	Benefit likely The clinical evidence demonstrates the successful use of FibroScan in a variety of settings (GP, community clinics, drug/alcohol centres, homeless centres, mobile outreach services). Clinical experts advise that transient elastography would not be repeated in secondary care. Scanning outside a secondary care setting removes burden from hospitals (waiting lists, referral delays). Test failure, test reliability and patient habitus may result in patient requiring scan in hospital setting.
	Increase compliance	Benefit likely No directly comparative evidence to suggest that there is increased uptake of FibroScan in primary or community care than in secondary or specialist care setting. However clinical experts have

		advised that proportions not attending are lower in a non-hospital setting (10% vs. 40%).
	Avoid unnecessary referrals to secondary care	Benefit unclear Rates of referral to secondary care may depend on the pathway and threshold applied to the FibroScan outputs (as advised by experts). Increased uptake of transient elastography measurement in primary/community care setting, may lead to earlier detection and management, thus avoiding secondary care referrals. Clinical experts agree that use of the device has the potential to reduce burden on hospital outpatient clinics (EAC Correspondence Log, 2021). However, use of FibroScan in a primary or community care setting will not eliminate all referrals to secondary care; for example test failures, unreliable results, unavailability of devices (and XL+ probes) and application of thresholds will still require referral to secondary care.
	Requires less time	Requires less time to diagnosis: Benefit likely No direct comparator evidence directly supports this outcome. Different thresholds have been used across the published evidence, to support different diagnostic and referral pathways. However, due to higher attendance in a non-hospital setting, clinical experts have recognised the potential for FibroScan to detect liver disease earlier in the patient pathway (EAC Correspondence Log, 2021).
Abbreviations: EAC, external assessment centre		

8.1 *Integration into the NHS*

The included clinical evidence demonstrates the successful use of FibroScan across a range of settings (including GP practices, community clinics, drug or alcohol centres, homeless centres, mobile outreach services) with measurements taken by liver nurses and peer support workers. This demonstrates the versatility of the FibroScan device, and its likely ease of use. The experts have advised that FibroScan is used across a range of specialties including cardiology, dermatology, endocrinology, gastroenterology, heptatology, rheumatology as well as general practice, drug and alcohol, obesity care and cystic fibrosis teams (EAC Correspondence

Log, 2021). The clinical experts advised that local diagnosis is an additional benefit to patients (with fewer hospital visits and reduced wait times), with repeated measurements enabling ongoing monitoring in the community.

The majority of evidence included in this assessment report used older models of FibroScan (FS402, FS502) which are now no longer available, or did not report the model. Only one study using currently available models of FibroScan (FS430 mini+, Reinson *et al.* 2021) was identified by the EAC. However the Company have claimed equivalence in clinical, biological, and technical characteristics, and therefore equivalence of clinical evidence for all models of FibroScan. High levels of test failure with the M+ probe have been reported in obese populations, however access to XL+ probes is shown to reduce this.

The clinical experts advised that FibroScan is not currently available across regions of the UK (EAC Correspondence Log, 2021). A national UK survey of community liver disease management completed by 159 clinical commissioning groups (CCGs) carried out on behalf of the British Liver Trust (Jarvis *et al.* 2021) suggested that 25% of CCGs use transient elastography (FibroScan). Commissioning FibroScan in primary and community care is likely to save costs in a different setting (such as secondary care), which may act as a barrier to implementation. Furthermore, the clinical experts stated that approximately one third of FibroScan devices currently in primary or community care are older devices that cannot be upgraded and cannot calculate the controlled attenuation parameter (CAP) related to hepatic steatosis, EAC Correspondence Log, 2021. The EAC notes that none of the peer-reviewed publications included in the assessment report reported CAP as an outcome measure.

No specialised equipment is required to use FibroScan in primary or community care, other than a clinic room and a patient couch or bed. Echosens provides on-site training to all clinical staff operating FibroScan (half a day for maximum of three trainees). Training comprises theory (60 to 75 minutes) and practical (120 to 180 minutes depending on the number of participants), with each trainee required to perform at least 3 full examinations

on 3 different volunteers. The clinical experts confirmed that anyone can be trained to use FibroScan, with users gaining proficiency very quickly. However, clinical experts did highlight a learning curve using the technology. One expert stated that users need to review the elastogram not just the numerical output from the FibroScan device, highlighting that an incorrect elastogram can lead to an inaccurate score (EAC Correspondence Log, 2021). One expert confirmed that review of the elastogram is useful to ensure that the probe is in the correct plane, an additional expert stated that review of the elastogram may be relevant if readings were unsuccessful or unreliable, an additional expert stated that elastogram review is required to ensure the readings are reliable and that elastogram review was included in the FibroScan training. The company confirmed that: *"future operators are trained to conduct a quality check of the elastogram during the training session".* Disinfection of the FibroScan ultrasound transducer is required after each use. The only consumable required to operate FibroScan is water-based jelly. No training is required for the patient.

The clinical experts have advised that FibroScan is used variably in primary or community care settings across the NHS. FibroScan is not currently available on NHS Supply Chain.

8.2 *Ongoing studies*

The Company identified one study from the UK where recruitment had completed (Appendix C1), for which the EAC was unable to find a publicly available record. The EAC searched clinicaltrials.gov (on 22/09/2021) and the ISRCTN Registry (on 23/09/2021) for "Fibroscan AND (primary OR community)" trials starting on or after 01/01/2016 when portable FibroScan devices, suitable for use in non-secondary care settings, were first available. Restricting the search by setting reduced the number of results to roughly 10% of those found when searching for "Fibroscan" alone. The EAC acknowledges that this is a limitation and that relevant studies outside of secondary care may have been overlooked. The EAC identified one additional

completed study using this approach (Appendix C1). No additional ongoing studies were identified through the EAC literature search.

Two ongoing studies from the UK were identified by the EAC (Appendix C2). Experts shared information on three additional studies:

- the Scarred Liver Project which is a programme of work that involves broad aspects of diagnostics, implementation and evaluation, which does not have a trial registration (hence not identified by the EAC search);
- the knowledge of liver fibrosis affect drinking behaviour (KLIFAD) study, which is a subset of an ongoing study identified by the EAC, and estimated to complete at the end of 2021 (ISRCTN16922410);
- the Integrated Diagnostics for Early Diagnosis of Liver Disease (ID-LIVER) study (conducted in Manchester), which is an observational study with target recruitment of 1200 patients attending a community liver assessment clinic and combines data from blood biomarkers, single nucleotide polymorphism analysis and faecal microbiome analysis from patients with liver disease in a database (NCT04666402). The trial registration mentions that the study population includes patients with fatty liver on ultrasound, however does not explicitly mention use of FibroScan (hence not identified in the EAC search).

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

The Company's search strategies for economic evidence were the same as the clinical evidence strategies, but with the added the terms 'cost' and 'economic'. These were appropriate to use, but a wider range of terms for this concept could have identified a greater number of results. The EAC did not carry out a separate economic literature search, as all economic evidence would have been identified within the EAC's clinical evidence search (Appendix A2).

Four studies were identified by the Company; summarised in Table 1 and reported in more detail in Section 2 of the Company Economic Submission. The EAC considered all four studies to have relevance to the decision problem, and did not identify any additional published economic evidence from a UK perspective.

The Company concluded that the economic evidence supported the claimed benefits of using FibroScan outside of a secondary care setting. These benefits include increasing detection of NAFLD with advanced fibrosis and cirrhosis, reducing unnecessary referrals to secondary care in low risk patients, and delivering cost savings. The Company did not use any parameters from the included economic studies to inform the *de novo* model.

Published economic evidence review

The EAC critically appraised the four relevant published studies using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau *et al.* 2013), Appendix D1. A summary of identified economic evidence is given in Table 15.

Table 15. *Summary of economic studies identified.*

Study reference	Methods and perspective	Population	Intervention(s)	Clinical and cost parameters	Summary results	EAC comments
Srivastava *et al.* (2019) UK	Cost-comparison analysis of five scenarios (two including FibroScan in primary care) using probabilistic decisional model simulation, from UK NHS perspective.	1,000 simulated patients with confirmed NAFLD. Average patient was 50 years old, with elevated transaminases.	Interventions: scenario 3 (FIB-4 and FibroScan) and scenario 5 (FibroScan alone), both in primary care. Other scenarios are scenario 1 (standard care, comparator), scenario 2 (FIB-4 and ELF), and scenario 4 (ELF alone), in primary care.	Clinical parameters from published evidence and expert opinion where needed. Cost parameters from published resources and local costing tariffs.	Total cost savings over 1 year for 1,000 modelled patients were £151,816 (scenario 3) and £26,889 (scenario 5), compared with standard care (scenario 1). Significant contributor to savings was reduction in secondary care referrals.	Did not conduct PSA.
Tanajewski *et al.* (2017) UK, Nottingham	Cost-effectiveness evaluation using decision tree and Markov model, informed by feasibility study, from NHS England perspective.	293 patients identified with risk factor for chronic liver disease in feasibility study from two primary care practices, with type 2 diabetes prevalence of 3.7% and obesity prevalence of 14.9%. Mean (SD) age was 68.4 years, and patients with history of excessive alcohol use were excluded.	Intervention: Risk Stratification Pathway (RSP) in which patients at high risk of developing liver disease are invited to attend for TE reading in community.	Clinical parameters from published evidence, expert opinion where needed, and feasibility study. Cost parameters from published evidence, UK local and national guidelines, international clinical practice guidelines from European Association for the Study of the Liver and American	Deterministic cost-effectiveness analysis found mean lifetime costs per patient of £9,017 for RSP, versus £8,505 for standard care. Probabilistic cost-effectiveness analysis found mean lifetime costs per patient of £10,307 (95% CI: £3,811 to £20,442) for RSP and £10,082 (95% CI: £3,494 to £20,793) for standard care. The cost	Cost difference from PSA (£225) different to point estimate cost difference (£512).

Study reference	Methods and perspective	Population	Intervention(s)	Clinical and cost parameters	Summary results	EAC comments
				Associated for the Study of Liver Disease, NHS reference costs, Personal Social Services Unit and NHS pay scales, and local finance departments.	difference from PSA was £225 (95% CI -£2,699 to £2,856).	
Serra-Burriel *et al*. (2019)	Cost-effectiveness analysis, tuned using diagnostic algorithm developed with conditional inference trees, based on previously published cost-effectiveness model (Tanajewski *et al*. 2017). Perspective "generated with provider-direct costs only", over time horizon of 30 years.	6295 patients from six cohorts, with 378 from the UK, undergoing TE. 6199 patients underwent successful TE (1.5% failed). Cohorts from Spain, Germany and Hong Kong included general population aged above 18 years, French cohort included general population above 45 years, cohort from Denmark included patients above 18 years at risk of liver disease from hazardous alcohol consumption, and UK cohort included patients with risk factors for chronic	Intervention: TE for detection and risk stratification for advanced chronic liver disease in adults with suspicion of NAFLD or ALD in primary care setting.	Exact source of clinical parameters not reported, but assumed to be a database from each study, including demographics, physical exam, clinical and laboratory parameters, and comorbidities, plus liver biopsy results (if available, n=352) including Kleiner, FIB-4 and NAFLD fibrosis. Source of cost parameters not reported (appendix referenced but not identified by EAC).	Cost results not reported separately for UK cohort, but reported numbers needed to screen (NNS) to identify one case, by risk factor. NNS for obesity is 2.7 (95% CI: 2.2 to 3.6), for diabetes is 3.9 (95% CI: 3.1 to 5.0), and for excessive alcohol use is 5.5 (95% CI: 4.5 to 7.3). Breakdown of fibrosis stages identified on biopsy, and diagnostic accuracy, also reported.	Only 6.0% (378/6295) of the included population was from the UK, in an at risk population. However, the modelled pathway is of relevance, and some of the results reported may be applicable to the economic case for FibroScan in the scope of this assessment.

Study reference	Methods and perspective	Population	Intervention(s)	Clinical and cost parameters	Summary results	EAC comments
		liver disease (hazardous alcohol use or type 2 diabetes). Mean age across cohort 54.7 years.				
Crossan *et al.* (2019) UK	Cost calculator of three scenarios (one including FibroScan in primary care), perspective not explicitly reported (assumed to be UK NHS).	Hypothetical cohort of 1,000 unselected patients with NAFLD, being tested for advanced fibrosis.	Intervention: scenario 2a (FibroScan in primary care after indeterminate FIB-4, with referral to tertiary care if fibrosis at F3 or above), and scenario 2b (FibroScan in primary care after indeterminate FIB-4, with referral to tertiary care if fibrosis at F3 or above, followed by liver biopsy and referral back to either tertiary or primary care).	Clinical parameters from published evidence, assumptions, NICE clinical guidelines for obesity, expert opinion. Cost parameters from published evidence, British National Formulary, expert opinion.	At 5% prevalence of advanced fibrosis, the mean total cost per person over a five year period of scenarios 2a and 2b were £963 and £839, compared with £1,100 for scenario 1 (all patients referred to tertiary care). At 15% prevalence of advanced fibrosis, the mean total cost per person over a five year period of scenarios 2a and 2b were £1,318 and £1,304, compared with £1,444 for scenario 1 (all patients referred to tertiary care).	Parameter sources not well reported. Also includes FibroTest and ELF as second-tier tests.

Abbreviations: ALD, Alcoholic liver disease; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 (index for liver fibrosis); NAFLD, non-alcoholic fatty liver disease; NNS, numbers needed to screen; PSA, probabilistic sensitivity analysis; RSP, Risk stratification pathway; SD, standard deviation; TE, transient elastography.

Results from the economic evidence

Three of the economic studies (Srivastava *et al*. 2019, Crossan *et al*. 2019, Tanajewski *et al*. 2017) were explicitly reported, or assumed to be, from the perspective of the NHS in England or the UK.

Srivastava *et al*. (2019) and Crossan *et al*. (2019) were similar, with both modelling a hypothetical cohort of 1,000 patients with NAFLD, over multiple scenarios involving FibroScan and other non-invasive tests in primary care. Both studies reported cost savings. Srivastava *et al*. (2019) reported total per-person cost savings, over one year, of £151.83 when FibroScan was used in conjunction with FIB-4, and £26.89 when FibroScan was used alone, compared with standard care. Crossan *et al*. (2019) reported mean total costs per person over five years at advanced fibrosis prevalences of 5% and 15%. Two scenarios included FibroScan; the first used FibroScan after an indeterminate FIB-4 result, with referral to tertiary care with fibrosis at F3 or above, and the second extended this by following the tertiary care referral with a liver biopsy, and referral back to tertiary or primary care. These scenarios were compared with a scenario assuming all patients were referred to tertiary care. At 5% prevalence, the mean total costs per person over five years were £963 in the first scenario, and £839 in the second, compared with £1,100 for all patients being referred. At 15% prevalence, the mean total costs per person over five years were £1,318 and £1,304, compared with £1,444 for all patients being referred.

In contrast to Srivastava *et al*. (2019) and Crossan *et al*. (2019), who reported on a cohort with known liver disease, Tanajewski *et al*. (2017) modelled patients with risk factors for liver disease, and compared a risk stratification pathway (RSP), where those with known risk factors were invited to have FibroScan in primary care, with standard care. They reported lifetime costs per patient of £9,017 for RSP, versus £8,505 for standard care, using deterministic cost-effectiveness analysis. Probabilistic cost-effectiveness analysis found mean lifetime costs per patient of £10,307 (95% CI: £3,811 to £20,442) for RSP and £10,082 (95% CI: £3,494 to £20,793) for standard care; therefore a cost difference of £225 (95% CI: -£2,699 to £2,856). Given the

wide confidence intervals, that the confidence interval for the cost difference crosses zero, and that the results represents lifetime costs, no conclusions may be drawn on the cost-effectiveness of using FibroScan in the population, and pathway, reported.

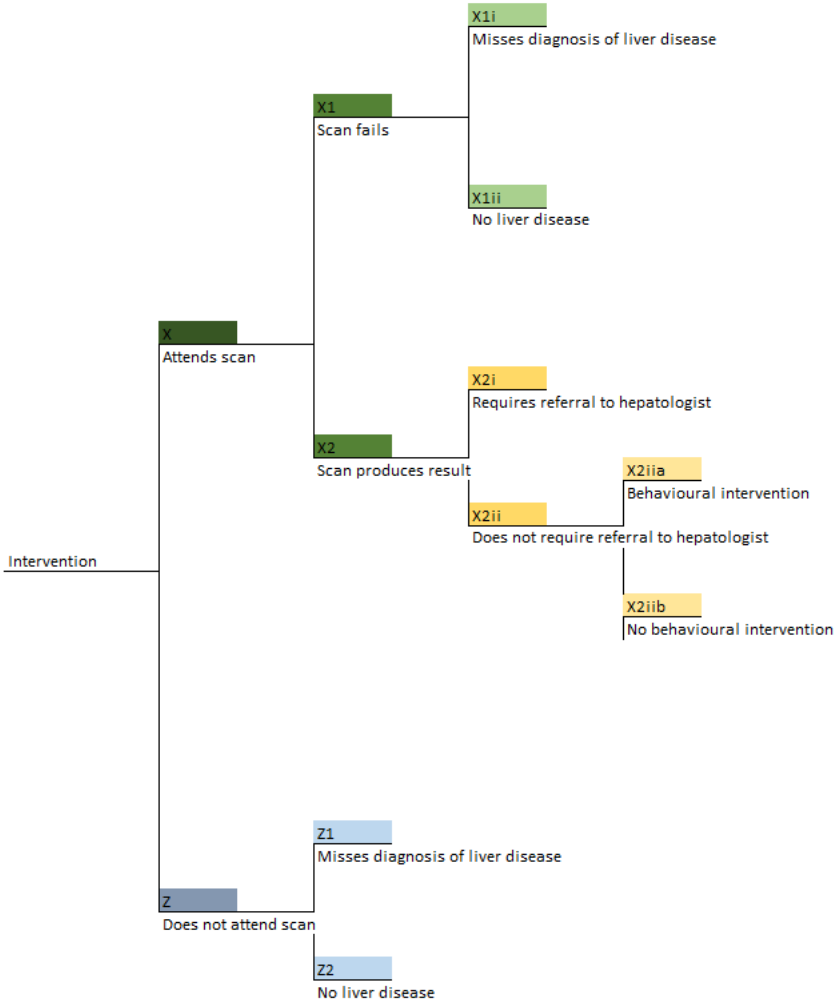
Serra-Burriel *et al*. (2019) did not report costs specific to the cohort from the UK, but reported the numbers needed to screen to detect one case with fibrosis stage of F2 or higher were lowest in the obese subgroup at 2.7 (95% CI: 2.2 to 3.6). The numbers needed to screen in the diabetes cohort was 3.9 (95% CI: 3.1 to 5.0), and for excessive alcohol use was 5.5 (95% CI: 4.5 to 7.3).

9.2 *Company de novo cost analysis*

Economic model structure

The Company developed a *de novo* cost consequences model in an executable Excel spreadsheet, described across 13 worksheets. The EAC critically appraised the *de novo* model and its narrative description in the Company's Economic Submission using the Drummond checklist (Drummond *et al.* 1996), Appendix D2. The model included 24 parameters and 7 costs, and compared the use of FibroScan outside of secondary or specialist care, with its use in secondary or specialist care. The cost-consequences model consisted of a single decision tree, following a patient from the time the decision is made using FIB-4 to determine whether FibroScan is indicated, through testing in either secondary or specialist care, or outside of secondary or specialist care. The structure of each arm is identical, with patients either attending or not attending their scan. For patients who do not attend their FibroScan appointment, their pathway ends with either no liver disease or a missed diagnosis of liver disease. These same endpoints are reached if the patient attends for FibroScan, but the scan fails and no result is available. If a reliable result is produced, the patient is either referred to a hepatologist, or not referred to a hepatologist, and if they are not referred, they may undergo a behavioural intervention or have no further management. Embedded macros were used for deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). The structure of the model is shown in Figure 4.

Figure 4: Structure of the *de novo* economic model [taken from Company model]



The EAC considers the approach taken by the Company, in developing a *de novo* decision tree using a cost-consequences framework, to be appropriate. Only two of the published economic studies (Srivastava *et al*. 2019 and Crossan *et al*. 2019) could have supported this economic evaluation. Crossan *et al*. (2019) modelled pathways over a five year time horizon, with repeated testing in primary care for patients with fibrosis levels less than F3, and repeated follow-up in tertiary care for those with F3 fibrosis or higher. The EAC considered this pathway and time horizon more complex than necessary to assess the economic case for adopting FibroScan outside of secondary or specialist care. Srivastava *et al*. (2019) modelled a diagnostic pathway over a

one year time horizon, followed by a five year timeframe to assess longer term disease progression, complications, and outcomes. The EAC also considered this more complex than necessary for the decision problem (where the same FibroScan device would be used in the same at-risk population, but with measurement taken in different setting by different staff). However, the EAC considered that aspects of the first year of the pathway modelled by Srivastava *et al*. (2019) should have been incorporated into the Company's *de novo* model, in particular the referral to specialist care in case of a failed reading. When asked to describe the steps taken after an invalid FibroScan reading in primary care, the clinical experts indicated a referral to secondary or specialist care was likely (EAC Correspondence Log, 2021).

Population

The Company defined the population, broadly in line with the scope, as "people having FibroScan to assess for liver fibrosis or cirrhosis (as per current NHS practice)." The Company assumed that the indication for FibroScan was a FIB-4 score in the "high risk" range. This is in line with the BSG Guidelines for NAFLD, although this also suggests using the NAFLD Fibrosis Score. There are other indications for using FibroScan, as reported by the literature (Table 4), the Company, and the clinical experts (EAC Correspondence Log, 2021). For example these may include ELF, AST to ALT ratio, BMI, AUDIT questionnaire, presence of comorbidities such as diabetes, obesity and hypertension, use of certain medications (for example, tamoxifen and methotrexate), or family history of liver disease. One clinical expert advised that blood markers have very good negative predictive value for ruling out liver disease, but poorer positive predictive value for ruling in significant disease (EAC Correspondence Log, 2021).

The Company further clarified the population as people with:

- Non-alcoholic fatty liver disease;
- Suspected non-alcoholic fatty liver disease (for example, those with metabolic syndrome or type 2 diabetes);
- Alcohol-related liver disease;

- Suspected alcohol-related liver disease (for example, those with hazardous alcohol use); or
- Hepatitis infection.

The submitted *de novo* model is also able to perform subgroup analysis on people with non-alcoholic fatty liver disease, alcohol-related liver disease, and hepatitis infection.

For the purposes of this assessment, its is assumed that the patients currently being referred for transient elastography in secondary or specialist care, would be the same people offered transient elastography measurement within a primary or community care setting. However, it is plausible that if FibroScan was more readily available in primary care, that GPs may choose to use it in broader populations. The Company's "cost per scan" model may also require wider use; "cost per scan" model in a non-hospital setting is £58, with a minimum of 25 scans per month, minimum contract term of 36 months. From NHS Reference Costs, a total of 3,561 ultrasound elastography (HRG RD48Z within the diagnostic imaging "IMAG" datasheet) investigations were conducted in outpatients 2019/20. Only 11 non-hospital centres would be required (at 25 per month) to achieve 3,561 scans in a 12 month period. However this is an upper estimate because HRG RD48Z is not specific to FibroScan (and may include elastography conducted on ultrasound machines), and is not restricted anatomically to the liver (for example, ultrasound elastography may also be used on the breast, prostate and thyroid). Therefore, the definition of "at risk" patients and eligiblility criteria for transient elastography measurement in a primary or community care setting, and the subsequent criteria for referral to secondary or specialist care (following transient elastography measurement in primary or community care) should be explicitly defined.

Intervention and comparator

The Company defined the intervention and comparator with no deviation from the published scope. The intervention is "FibroScan done outside secondary or specialist care (for example, GP or community services)", and the comparator is "FibroScan done in secondary or specialist care".

Outcomes

The outcomes influencing the costs of the use of FibroScan are: the proportion of patients scheduled for scans who actually attend, the prevalence of liver disease requiring referral to hepatology, and the prevalence of liver disease not requiring referral to hepatology, but requiring behavioural intervention.

The Company also reported changes in other outcomes between FibroScan used in secondary or specialist care, and FibroScan used outside of secondary or specialist care:

- Number of referrals to hepatologist after scan;
- Number of referrals to behavioural intervention;
- Missed diagnosis of liver disease; and
- Total number of visits to hepatology department.

There are further outcomes of relevance to the decision problem that were omitted by the Company. The only treatment costs included were for behavioural interventions in those not requiring referral to hepatology, which the EAC considered appropriate, as relatively few patients would likely be referred to hepatology, and there would be many options for further investigations or treatment, perhaps spanning many months or years, which would add unnecessary complexity to the model. There are also potential benefits of moving FibroScan out of secondary or specialist care, that are not captured by the Company's *de novo* model. For patients, these include reduced waiting times for FibroScan, and shorter time to diagnosis, and for healthcare providers, there may be fewer emergency care admissions with decompensated cirrhosis, if cases of liver disease are identified sooner. However, the EAC acknowledges the limited data to support these outcomes, and considers their exclusion from the model appropriate.

Time horizon

The Company reported having used a time horizon of less than one year, as the FibroScan test and decisions regarding treatment should be completed within this time, to allow any differences between model arms to be captured.

As treatment outcomes have been omitted from the model the EAC considers this time horizon appropriate. However, as FibroScan measurement is repeated in some patients (with frequency dependent upon severity of fibrosis), the cost saving presented in the Company model may represent a lower estimate. Due to the short time horizon, the Company applied no discount rate, which the EAC considered appropriate.

Assumptions

The Company summarised the assumptions made in their *de novo* model, in Table 2 of the Company Economic Submission, summarised by the EAC in Table 16.

Table 16: Assumptions made by the Company to support *de novo* model

Assumption (from Company submission)	Company justification	Company source	EAC comment
Once patient has attended scan, the proportion requiring referral to a hepatologist is the same regardless of whether the scan is received inside or outside of secondary care	The underlying prevalence of liver disease is not affected by the care setting. Furthermore, the ability of the scan to identify liver disease is the same regardless of care setting	No source provided.	The EAC considers the justification for this assumption to need clarification. The prevalence of liver disease may vary by care setting. People presenting directly to secondary care (via A&E, for example) may be more likely to have liver disease requiring hepatology referral, and are not excluded by the scope, nor by the population defined by the Company. The EAC would suggest the population being assessed is people identified in primary care as requiring FibroScan to assess for liver fibrosis or cirrhosis. The ability of the scan to identify liver disease may also differ by setting if a suitable probe is not available in primary care (see assumption below).
Once patient has attended scan, the failure rate of the scan in returning an image is the same,	The likelihood that the scan fails to return a liver stiffness measurement is	No source provided.	The EAC considers it appropriate to assume that a fully trained, competent user, who performs enough scans to

regardless of whether the scan is received inside or outside of secondary care	dependent on the patient characteristics, and not the care setting.		maintain their skills, and has access to the same device and probes, will achieve the same success, regardless of setting. This is supported by comments from the clinical experts, although they also highlighted a learning curve for new users (EAC Correspondence Log, 2021). The EAC has noted from Hospital Episodes Statistics data that 3,688 ultrasound elastography investigations were recorded in 2019 to 2020. The EAC assumes this includes FibroScan, and non-FibroScan ultrasound elastography including that performed on other organs. As this is likely an upper estimate, the EAC is concerned about the level of adoption needed outside of secondary or specialist care to maintain user skills and also meet the Company's Pay Per Scan requirement of 25 scans per month (3,688 scans per year is 307 per month, and equates to a maximum of 12 centres performing 25 scans each). It is likely that the referral criteria would need to be broadened to meet these requirements, which is not accounted for in the model.
In the current submission, the likelihood of a patient attending the scan is assumed to be the same across all subgroups.	Patient behaviour is not expected to differ by subgroup. However, further analyses of the Southampton CCG pilot study may provide subgroup-specific information on attendance rates in the near future.	No source provided.	The EAC acknowledges that the Company made this assumption in the absence of subgroup-specific evidence from the Southampton CCG pilot study. However, the EAC considers it inappropriate, and considers it plausible that different subgroups would have different levels of investment in their health and therefore different willingness to attend for diagnosis and treatment. This is supported by comments

			from the clinical experts (EAC Correspondence Log, 2021) and findings reported by Knight *et al*. (2020) that, for example, patients with type 2 diabetes are likely to attend healthcare appointments due to regular ongoing disease monitoring. Other groups, with no prior risk factors or indication of ill-health, may be surprised to be invited and more likely not to attend. El-Gohary *et al*. (2018) also reported different levels of attendance for FibroScan in primary care, which depended on whether patients were referred by their GP, identified using their medical records as being high risk, or deemed at risk following completion of the AUDIT questionnaire.
If the patient does not require a referral to a hepatologist, the likelihood of requiring a behavioural intervention is the same inside or outside of secondary care	Treatment received when a scan shows no requirement for a hepatologist referral is the same regardless of care setting	No source provided.	The EAC considers this an appropriate assumption, provided there are consistently applied guidelines for offering a behavioural intervention. However, the EAC sought clinical expert opinion on the appropriateness of assuming the behavioural intervention would be delivered by a GP, after referral back to primary care. Clinical experts generally agreed that either the behavioural intervention is delivered immediately following FibroScan at the same appointment, or that it would be sensible to do so (EAC Correspondence Log, 2021).
The proportion of patients requiring referral for specialist treatment within those who have liver disease is assumed to be the same in the subgroups as in the overall population	Data on referrals was available for the overall population from the Southampton CCG pilot study, however, subgroup-specific information was not. The underlying	No source provided.	In the absence of further evidence, the EAC considers this an appropriate assumption. However, the EAC notes that different subgroups may present for diagnosis and treatment at different stages of disease, which

	prevalence of liver disease does differ between subgroups, but the distribution of severities at the time of identification was assumed to be the same.		may increase referrals in some subgroups.
In secondary or specialist care, patients identified as requiring specialist treatment are assumed to be invited for a follow-up visit to initiate the treatment.	In line with UK clinical practice	No source provided.	The EAC sought clinical expert opinion and received varying responses. Some indicated that in secondary care, FibroScan and treatment initiation could be carried out at the same visit. Others indicated that the majority would return for a follow up appointment, or that it depends on the cause of liver disease, or the availability of the technology (EAC Correspondence Log, 2021). However, given the heterogeneity in responses, the EAC considers it appropriate to assume that those having FibroScan in secondary care and needing treatment, would be invited for a follow up appointment with hepatology.
If the patient attends the scan, then for a small proportion of patients the scan may fail to produce results. In these cases… the diagnosis will be missed and the liver disease will remain untreated for the proportion of patients with underlying liver disease.	Not reported in assumptions table, therefore no justification provided.	No source provided.	The EAC considers this assumption incorrect. The clinical experts indicated that if FibroScan failed in primary care, a further fibrosis test, or secondary or specialist care should be sought (EAC Correspondence Log, 2021).
The Company assumes the starting point for the model is a FIB-4 test used to stratify patients into needing FibroScan investigation or not.	Not reported in assumptions table, therefore no justification provided.	No source provided.	The EAC acknowledges lack of national guidance on referral criteria for FibroScan in secondary care. Clinical experts and published evidence suggest that referral criteria could be based on, for example: FIB-4, AST/ALT, NAFLD fibrosis

			score, BMI, diagnosis of Type 2 diabetes, alcohol AUDIT questionnaire, patients at risk of hepatitis.
The Company assumes that FibroScan, used in any setting, has maximum sensitivity and specificity, and there are no false positives or false negatives.	Not reported in assumptions table, therefore no justification provided.	No source provided.	The EAC considers it appropriate that false positives and negatives were not modelled, as one clinical expert commented that true false positive and negative rates are not known (EAC Correspondence Log, 2021), and this would introduce further uncertainty into the model. The experts agreed that FibroScan has high negative predictive value, and using a threshold of 15 kPa, sensitivity of around 70%. However, it was estimated that around 50% of cirrhosis cases are identified through events, rather than testing, and repeated testing of those at risk would minimise the chance of missing cases. Experts generally considered the impact of false positive results to be better than false negatives, as patients may be reassured that they do not have fibrosis or cirrhosis if they have been thoroughly investigated, and if lifestyle advice is given, this will do no harm but may be beneficial in those at risk. However, one expert noted that patients may be falsely reassured by a false positive result, that they are healthy and do not need to take action to reduce alcohol consumption, or lose weight, for example (EAC Correspondence Log, 2021).
Abbreviations: A&E, accident and emergency; AUDIT, alcohol use disorders identification test; CCG, clinical commissioning group; EAC, external assessment centre			

Validation of the economic model

In the Economic Submission, the Company reported that the model underwent conceptual and technical validation. Conceptual validation was performed by comparing pathways described in the Southampton CCG pilot study (unpublished, details shared by Company), and by consultations with Echosens' clinical experts with experience of patient referral practices in the UK. A separate person, who had not been involved in the original programming, did technical validation by checking the calculations and formulae, and another member of the team checked the parameter values used as inputs to the model.

For verification, the EAC was able to replicate the Company model using R programming language (R Core Team, 2020) and the *rdecision* package (version 1.1.0) (Appendix E1).

Economic model parameters

Clinical parameters and variables

The Company reported the values for the clinical parameters and variables used in the model in Table 3 of the Company Economic Submission. A variety of sources were used, as summarised in Table 17.

Table 17: Clinical parameters used in the Company's model and any changes made by the EAC

Variable [arm of model]	Company value, range and distribution (if applied)	Source	EAC comment
Does not attend scan [Non-hospital setting]	11% Univariate: range 9% to 14% PSA: Beta (α=66, β=533)	Southampton CCG	This value is in broad agreement with the advice gained from clinical experts (EAC Correspondence Log, 2021). However, the uptake reported in the published literature was between 38% and 97% from 5 studies in GP, clinic, and homeless hostel settings. This corresponds to non-attendance between 3% and 62%, which is not covered by the PSA distribution stipulated by the Company (which corresponds to a 95% CI of 8.6% to 13.6%. This will be addressed in sensitivity analysis.

Variable [arm of model]	Company value, range and distribution (if applied)	Source	EAC comment
Does not attend scan [Hospital setting]	20% Univariate: range 16% to 24% PSA: Beta (α=79.8, β=319.2)	Southampton CCG	There is no published comparative data to support this. The EAC notes that parameters used to describe the beta distribution are incorrect. An email provided by the Company alongside their Economic submission states the following parameters should have been used: α=46, β=170. This corresponds to a 95% CI of 16.1% to 27.0%. However, clinical experts reported non-attendance proportions of up to 40% in secondary care (EAC Correspondence Log, 2021).The EAC therefore recommends that the base-case estimate be increased in line with this, and the uncertainty addressed in sensitivity analysis.
Scan produces a result [Both arms]	95% PSA: Beta (α=4.05, β=0.21)	Assumption based on scan fails ratios	The EAC was unable to verify the parameters due to lack of reporting of source. The EAC notes that there are two elements to consider: 1) failure to obtain 10 valid measurements (in line with FibroScan instructions for use). This ranged between 1.7% (Reinson *et al.* 2021) and 2.2% (Harman *et al.* 2018) in broad screening populations in the clinical evidence; 2) unreliability based on IQR/median ratio (in line with FibroScan instructions for use) which was approximately 4.9% (Harman *et al.* 2018). The EAC notes that test failure and test unreliability were both much higher in obese patients. Therefore, the EAC recommends that inability to produce a result includes the combination of test failure and test unreliability of 7%, and that this is increased in sensitivity analysis. That is, scan produces a result in 93% of cases in primary care. The EAC would suggest that test failure related to patient habitus will be the same regardless of setting. However test failure due to lack of access to XL+ probe, and reduced experience of the technology

Variable [arm of model]	Company value, range and distribution (if applied)	Source	EAC comment
			may result in test failure being increased outwith a hospital setting. Test failurewill be addressed in two-way sensitivity analysis.
No liver disease [Both arms]	55% PSA: Beta (α=505, β=405)	El-Gohary *et al*. (2018)	The EAC notes that the Company has assumed that all patients in the El-Gohary *et al.* (2018) study with a transient elastography value above 6 kPa are considered to have liver disease (405/910), therefore leaving 55% (505/910) with no liver disease. The EAC also notes that the beta distribution parameters stipulated by the Company correspond to a narrow 95% CI of 52.3% to 58.7%, but acknowledges that this is derived from the counts observed in the study and can therefore be justified. However, if a threshold of 8 kPa was used (in line with the majority of studies identified in the clinical evidence) then the proportion considered to have liver disease would be 20% (185/910), and therefore 80% (725/910) with no liver disease may be more appropriate. Thresholds used in different publications are applied in scenario analysis, to inform proportions referred to hepatology, behavioural intervention or no further intervention. Harman *et al.* (2018) identified elevated liver stiffness (at least 8 kPa) in 230/899 patients, that is no liver disease in 74%. Harman *et al.* (2018) includes subgroup analysis: hazardous alcohol use, type 2 diabetes, hazardous alcohol use and type 2 diabetes, and elevated ALT levels. However the EAC would recommend a different three-tiered threshold approach (based on referral pathway described in Chalmers *et al.* 2019 – see below).
Requires referral to hepatologist [Both arms]	23.6% PSA: Beta (α=126, β=407)	Southampton CCG	The EAC notes that the 23.6% from this source could be referred to as the proportion with liver disease, as individuals without liver disease on FibroScan are unlikely to be referred to hepatology unless there are other concerns (and therefore is likely double counting with parameter above from a different source).

Variable [arm of model]	Company value, range and distribution (if applied)	Source	EAC comment
			The EAC would instead recommend a three tiered threshold approach, in line with the pathway described by Chalmers *et al.* 2019) based on liver stiffness: - Less than 8 kPa: no further referrals/investigations (76.9%; 740/962) - Between 8.0kPa and 14.9 kPa: provide behavioural advice, repeat 3-5 years (17.2%; 165/962) - 15 kPa or higher: refer to hepatology (5.9%; 57/962)
Behavioural intervention	100% Range 90% to 100%	Assumption	The EAC would recommend a three tiered approach, as described by Chalmers *et al*. (2019), and stated above. The EAC notes that biopsy is not included explicitly as an outcome, and assumes that this has been excluded to simplify the model due to the assumption that the proportion being referred for biopsy will be the same in both arms. The EAC also considers that it would apply to a small proportion of patients, and that it would take place after referral to hepatology.
Abbreviations: ALT, alanine aminotransferase; CCG, clinical commissioning group; CI, confidence interval; EAC, external assessment centre; PSA, probabilistic sensitivity analysis			

Resource identification, measurement and valuation

The cost parameters used in the Company *de novo* model are summarised in Table 18.

Table 18: Cost parameters used in the *de novo* model

Cost parameter	Company value (distribution, if applied)	Source	EAC comment
FibroScan "Go" (230) – Pay Per Exam outside of secondary/specialist care	£70.00	Company Economic Submission	Company confirmed error in economic model, should be £58 (EAC Correspondence Log, 2021). The EAC notes that this cost differs from the cost of FibroScan applied in primary care assumed in published economic evidence; ranging from £37.30 (Tanajewksi *et al.* 2017) to £47.00 (Crossan *et al.* 2019), and it cannot be assumed that the reported studies would remain cost saving if the FibroScan cost of £58.00 in primary care was applied.
15 minutes of staff time to perform and evaluate scan outside of secondary or specialist care	£10.50 (Range: £8.44 to £12.56)	£42.00 per hour, PSSRU Unit Costs of Health and Social Care 2020 Nurse (GP practice) incl. qualification costs	Company clarified that the hourly cost was obtained from Table 10.2 of the PSSRU Unit Costs 2020 report (EAC Communication Log, 2021). For its base case, the EAC instead used a cost of £38.00 per hour, which excludes qualification costs, in line with the indication in the Company's economic submission that FibroScan could be used by suitably trained healthcare assistants, therefore negating the need for nursing qualifications.
Cost of FibroScan outside of secondary or specialist care	£80.50 (Range: £64.72 to £96.28)	Cost per scan (£70.00) and staff time to perform and evaluate scan (£10.50)	Amended to £68.50 when exploring the Company model using the correct pay per scan model cost as above. The EAC used £67.50 in its base case, as above.

Cost parameter	Company value (distribution, if applied)	Source	EAC comment
Cost of FibroScan in secondary or specialist care	£43.93	National Schedule of NHS costs 2019-20 IMAGOP RD48Z; Ultrasound Elastography	Company also confirmed that FibroScan is not currently available in secondary care on a pay-per-scan basis (EAC Correspondence Log, 2021). However, the Company have used HRG bundled cost. HRG code RD48Z for ultrasound elastography may include other organs or non-FibroScan elastography (that is, the HRG code is not exclusive to FibroScan used for liver). Within 2019-20, the activity for this HRG code was 3,561 in outpatients, representing a weighted average cost of £61.98 each (NHS Reference Costs, 2019-20, HRG RD48Z; "IMAG" worksheet). However, this included a relatively small number of investigations from a small number of centres. The EAC therefore concludes that the £43.93 used by the Company is appropriate for the base case, but will increase this to £61.98 in scenario analysis. The EAC also applied this cost to the "Further Tests" branch in both arms of its base case, where FibroScan has failed. The EAC considers this an appropriate estimation as non-FibroScan ultrasound elastography may be used, or this may be an appropriate average between a cheaper blood test or more expensive imaging modality.

Cost parameter	Company value (distribution, if applied)	Source	EAC comment
Staff time to perform and evaluate scan in secondary or specialist care	£93.19	National Schedule of NHS costs 2019-20 306 Hepatology WF01B; Non-Admitted Face-to-Face Attendance, First (Non- Consultant led)	Staff time to perform and evaluate scan is already incorporated within the HRG bundled cost above (RD48Z) and therefore this cost should be removed to avoid double counting. [This is the consequence of comparing a bundled HRG cost from secondary care, with a microcosting in a non-hospital setting where an HRG code does not currently exist].
Cost for scan in secondary or specialist care	£137.12	Cost per scan (£43.93) and staff time to perform and evaluate scan (£93.19)	Cost of scan in secondary care is represented by HRG bundled cost, additional staff time costs not required (as above).
Cost of missed appointment in secondary or specialist care.	£93.19 (Range: £74.92 to £111.45)	National Schedule of NHS costs 2019-20 306 Hepatology WF01B; Non-Admitted Face-to-Face Attendance, First (Non- Consultant led)	No changes required. Howeve, the EAC notes that the Company model did not account for costs of missed appointments in the non-secondary care arm. For its base case, the EAC assumed the cost of a missed appointment in each arm would be the same as if the appointment had been attended. In scenario analysis, the EAC considered the cost of a missed appointment to be nurse time only. In primary care, this was 15 minutes at £38.00 per hour (as above), and in secondary care was 15 minutes at £50 per hour (PSSRU Unit Costs 2020; Hospital based nurse, band 6).
Referral to hepatologist from outside of secondary or specialist care	£207.86 (Range: £167.12 to £248.60)	National Schedule of NHS costs 2019-20 306 Hepatology WF01B; Non-Admitted Face-to-Face Attendance, First (Consultant led)	No changes required.

Cost parameter	Company value (distribution, if applied)	Source	EAC comment
Follow-up visit to hepatologist after scan in secondary or specialist care	£164.75 (Range: £132.46 to £197.04)	National Schedule of NHS costs 2019-20 306 Hepatology WF01A; Non-Admitted Face-to-Face Attendance, Follow-up (Consultant led)	No changes required. The EAC has also used this value in a scenario analysis where it is assumed that patients requiring behavioural intervention, receive this in the same setting as FibroScan. A further scenario assumes the intervention is delivered in secondary care by a telephone call and costs £89.52 (NHS Reference Costs, 2019-20; Consultant led, HRG WF01C Non-admitted face-to-face attendance, follow-up).
GP consultation	£39.23 (Range: £31.54 to £46.92)	PSSRU Unit Costs of Health and Social Care 2020 General practitioner per patient contact lasting 9.22 minutes incl. qualification costs	Company clarified that this value was obtained from Table 10.3b of the PSSRU Unit Costs 2020 report (EAC Communication Log, 2021).
Abbreviations: EAC, external assessment centre; HRG, Health Resource Group; PSSRU, Personal Social Services Research Unit			

Sensitivity analysis

Deterministic sensitivity analysis

The Company used univariate deterministic sensitivity analysis, varying model parameters individually according to their 95% confidence intervals where available, or assuming 10% variation of the mean. The Company did not vary all individual cost parameters, but where appropriate, instead varied composite pathway costs associated with chance nodes in the model, as given in Table 18. This was said to account for potential differences in, for example, the number of visits required, or the length of time required for scanning individual patients.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was used to account for combined variability in outcomes due to parameter uncertainty. Parameter estimates were randomly sampled 1,000 times, from probability distributions given in Table 17 and Table 18, to determine total scan costs per patient. The EAC notes that "No liver disease" was included twice in the PSA, separately for those attending the scan and those not attending the scan. This may have inappropriately widened the 95% confidence interval of cost differences in PSA.

Subgroup analysis

The Company reported separate results for three subgroups using data from El-Gohary *et al.* (2018):

- Non-alcoholic fatty liver disease;
- Alcohol-related liver disease; and
- Hepatitis-related liver disease.

The proportion of patients with no liver disease and the proportion referred to a hepatologist varied for each subgroup.

9.3 *Results from the economic modelling*

Base case results

In the Company's base case, the use of FibroScan outside of secondary or specialist care was £139.65 per person, compared with £180.70 per person in secondary or specialist care, resulting in an overall cost-saving per patient of £41.05, Table 19. Cost savings were driven by reduction in scanning costs and fewer missed appointments when using FibroScan outside of a hospital setting.

Table 19: Summary of base case results

	Company estimate*		
	Mean cost per patient per scan using FibroScan outside of secondary or specialist care	Mean cost per patient per scan using FibroScan in secondary or specialist care	Difference (Outside of secondary care minus within secondary care)†
Scan costs	£71.63	£109.70	-£38.06
Missed appointment costs	£1.16	£18.64	-£17.48
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£25.32	£22.77	£2.56
Total (per patient)	**£139.65**	**£180.71**[&]	**-£41.05**

* Taken from Table 9 of Company's Economic Submission.
[&] Corrected by the EAC from £180.57, note further discrepancies due to rounding.
† Negative values (shaded green) indicate a cost saving.

In the base case, the Company reported more referrals for hepatology and behavioural interventions in those receiving FibroScan outside of secondary or specialist care, Table 20; this was a direct consequence of a higher proportion of patients attending a non-hospital setting.

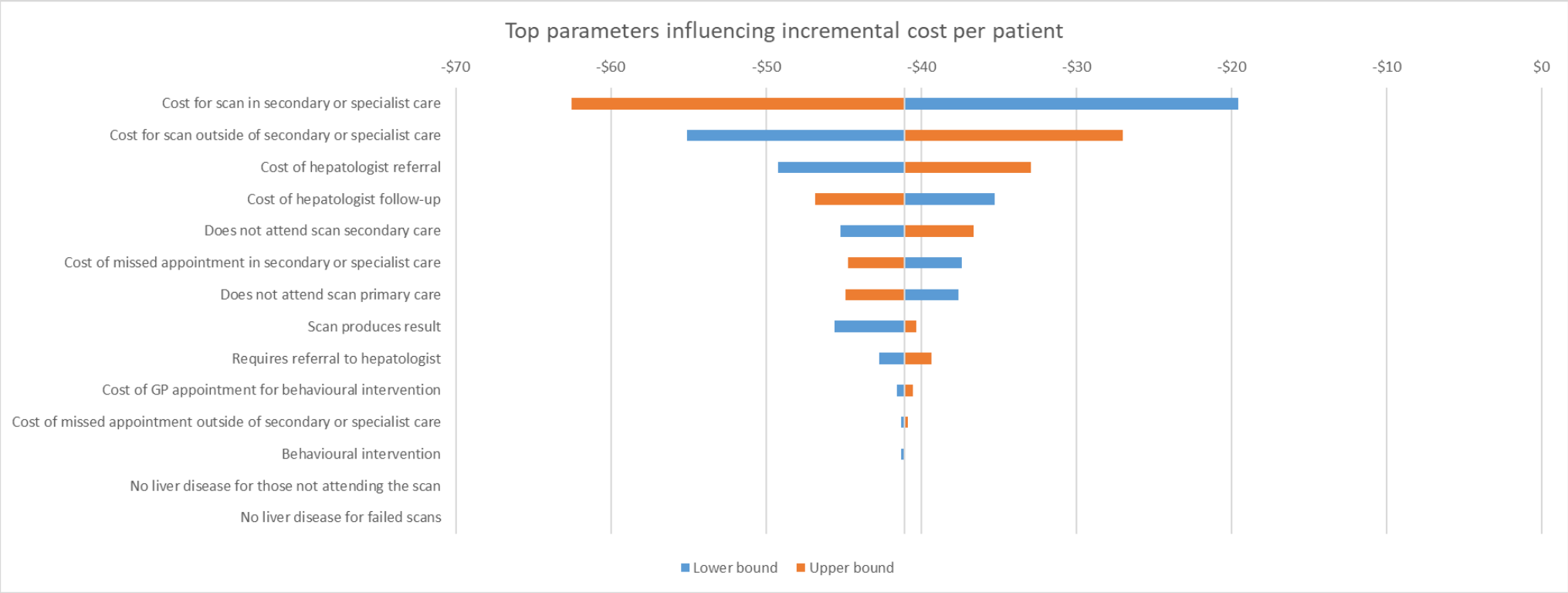
Table 20: Resource use in base case

Resource	FibroScan outside of secondary or specialist care	FibroScan in secondary or specialist care	Difference (Outside of secondary care minus within secondary care)
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.07	0.11	-0.04
Total number of visits to hepatology department	0.20	0.98[&]	-0.74
[&] Corrected by the EAC from 0.94, as failed scans in secondary care had not been counted as visits to the hepatology department in the Company model.			

Sensitivity analysis results

In the Company's univariate deterministic sensitivity analysis, all results showed the use of FibroScan outside of secondary or specialist care to be cost saving, when compared to its use in secondary or specialist care. The tornado diagram (Figure 5) shows that the result is most sensitive to changes in the scanning costs in secondary or specialist care, followed by the scanning costs outside of secondary or specialist care.

Figure 5: Tornado diagram of Company's univariate deterministic sensitivity analysis [taken from Company model, EAC assumes costs are in GBP (£) and not dollars ($)]



The Company's probabilistic sensitivity analysis found the use of FibroScan outside of secondary or specialist care to be cost incurring in only 0.3% of simulations, with a mean difference in cost per patient between FibroScan outside of secondary or specialist care, and FibroScan in secondary or specialist care of -£41.44 (95% CI -£12.66 to -£71.44).

The Company reported that FibroScan used outside of secondary or specialist care was cost saving in all subgroups assessed, when compared to FibroScan used in secondary or specialist care, Table 21.

Table 21: Results of Company's subgroup analyses

Subgroup	Mean discounted cost per patient per scan using FibroScan outside of secondary or specialist care	Mean discounted cost per patient per scan using FibroScan in secondary or specialist care	Difference (Outside of secondary care minus within secondary care)
Patients with non-alcoholic fatty liver disease	£139.67	£180.70	-£41.03
Patients with alcohol-related liver disease	£134.86	£177.48	-£42.62
Patients with hepatitis-related liver disease	£173.11	£203.07	-£29.96

Additional results

The EAC explored the Company model by making the following changes, Table 22. Note that the Company confirmed that the incorrect cost of FibroScan in a primary or community care setting was applied in their original economic model (was £70, however should have been £58). Therefore, the EAC has applied this change in all subsequent analysis.

Table 22: EAC changes implemented in the Company model, and the effect of each change separately

Parameter	Basecase value (Company)	Updated value (EAC)	Cost of FibroScan in non-hospital setting	Cost of FibroScan in hospital setting	Cost difference (non-hospital – hospital)	EAC comment
Basecase	N/A	N/A	£139.65	£180.70	-£41.05	
Cost of FibroScan (primary/community)	£70	£58	£128.97	£180.70	-£51.73	Company confirmed error in "pay per scan" cost for FibroScan in primary/community care setting. Reduction in FibroScan scan cost, increases cost saving as expected.
Cost of FibroScan (secondary/specialist)	£43.93	£61.98	£128.97	£219.14	-£90.17	Weighted average of all outpatient appointments (n=3561, HRG: RD48Z) increases cost of ultrasound elastography in secondary or specialist care setting, increases cost saving
Remove staff costs associated with FibroScan interpretation*	£93.19	£0	£128.97	£87.51	+£41.46	Interpretation costs included in HRG (removed staff time costs to avoid double counting).
Attendance (primary/community)*	89%	75%	£110.35	£180.70	-£70.34	As there are no subsequent healthcare costs associated with non-attendance, increasing the probability of non-attendance increases cost savings.
		60%	£90.38	£180.70	-£90.32	
		45%	£70.41	£180.70	-£110.29	
Test failure (primary/community)*	5%	10%	£125.45	£177.94	-£52.49	As there are no subsequent costs associated with test failure in the Company model, increasing the probability of test failure increases cost savings.
		20%	£118.41	£172.43	-£54.02	
		30%	£111.37	£166.92	-£55.54	
Missed liver disease (primary/community)*	45%	40%	£128.97	£180.70	-£51.73	No cost consequence of "missing" liver disease.
		30%	£128.97	£180.70	-£51.73	
		20%	£128.97	£180.70	-£51.73	
Referral to hepatologist (primary/community)*	23.6%	15%	£116.65	£172.46	-£55.80	Reduction in referrals to hepatology increases cost savings.
		10%	£109.53	£167.69	-£58.16	
		5%	£102.40	£162.92	-£60.52	
Behavioural intervention (primary/community)*	100%	90%	£126.44	£178.42	-£51.99	Reduction in behavioural advice (some patients incorrectly referred) increases cost savings.
		80%	£123.90	£176.15	-£52.24	
		70%	£121.37	£173.87	-£52.50	
*Change in addition to Cost of FibroScan in primary/community care being £58						

EAC base case

The EAC made changes to the Company's model, to define its own base case, shown in Figure 6. Based on clinical expert opinion (EAC Correspondence Log, 2021), the EAC added a branch for follow up after a failed FibroScan test, in which it was assumed patients would be referred from primary care to secondary care for further tests, or would undergo further tests if they had the first FibroScan test in secondary care. The EAC also assumed that a patient referred from primary care to secondary care following a failed FibroScan may fail to attend, and made further changes to the model to reflect this. It is assumed in the base case, and sensitivity and scenario analyses, that the probability of attending in secondary care is the same regardless of whether the patient is attending secondary care for a first FibroScan, or further tests after a failed FibroScan in primary care. The EAC acknowledges that attendance proportions may vary, however, there is no published comparative data to inform this. The EAC assumed that all patients who failed to attend their scan had unknown outcomes, and did not assume prevalence of liver disease or no liver disease in this population. The results from the EAC base case are reported in Table 23.

Figure 6: Model structure of EAC base-case

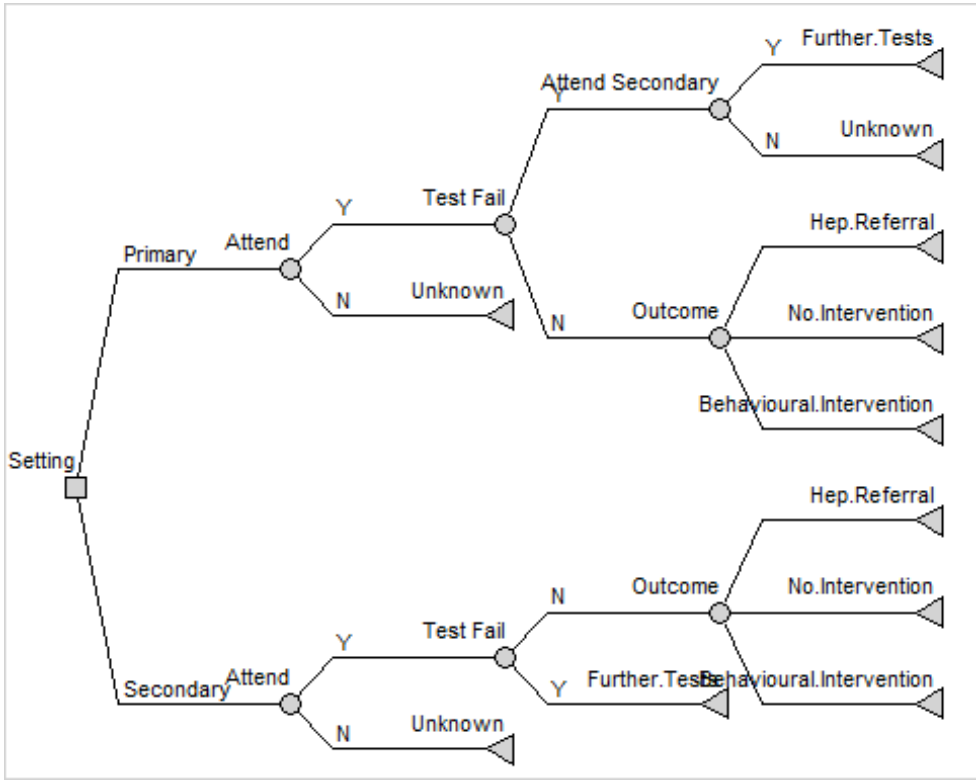


Table 23: EAC base case results

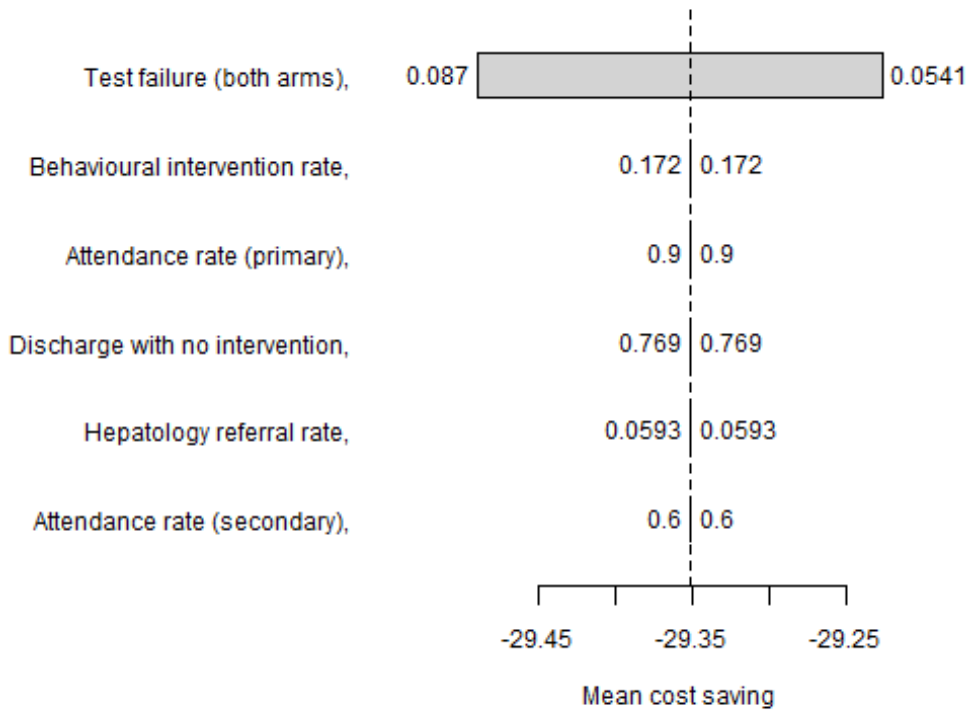
	Mean cost per patient per scan using FibroScan outside of secondary or specialist care	Mean cost per patient per scan using FibroScan in secondary or specialist care	Difference (Outside of secondary care minus within secondary care)†
Total cost per patient	£80.57	£51.21	£29.36
Patients with unknown outcomes	125	400	-275
Costs due to missed appointments	£2,048.25	£17,572.00	-£15,523.75
Patients referred to hepatology	50	33	17
† Negative values (shaded green) indicate a cost saving, or benefit in terms of fewer patients with unknown outcomes or a greater number of patients referred to hepatology.			

Sensitivity analysis results

The EAC did one way deterministic sensitivity analysis (DSA), including only probability of test failure, which was varied over its 95% confidence interval, with the rest of the variables set to their point estimates. All other variables were considered in other sensitivity analyses, but could not be aggregated and represented as distributions due to a lack of robust published data. The tornado diagram is shown in Figure 7.

The mean cost difference from probabilistic sensitivity analysis between primary care and secondary care (that is, mean cost in primary care, minus mean cost in secondary care) was £29.35 (95% CI £29.23 to £29.49) per patient, and no simulations were cost saving; however PSA has little value as only one parameter (test failure) had a distribution (beta) applied. To account for large uncertainties a range of scenario analyses were conducted.

Figure 7: One-way deterministic sensitivity analysis (DSA)



Due to large uncertainties, the EAC did two-way DSA, varying attendance proportions in primary care across the range reported in the clinical literature (that is, between 37% and 97%), and varying attendance in secondary care relative to this, Table 24. The use of FibroScan in primary care was not found to be cost saving under any combination of attendance in primary care and relative attendance in secondary care.

Table 24: Two-way sensitivity analysis of attendance proportions in primary or community care, and secondary or specialist care settings using EAC model.

	Attendance in primary care						
Relative attendance in secondary care	**37%**	**47%**	**57%**	**67%**	**77%**	**87%**	**97%**
0.9	£24.90	£25.26	£25.62	£25.98	£26.33	£26.69	£27.05
0.8	£25.35	£25.83	£26.31	£26.79	£27.27	£27.75	£28.23
0.7	£25.80	£26.40	£27.00	£27.60	£28.20	£28.81	£29.41
0.6	£26.25	£26.97	£27.69	£28.42	£29.14	£29.86	£30.59
0.5	£26.70	£27.54	£28.38	£29.23	£30.07	£30.92	£31.76
0.4	£27.14	£28.11	£29.08	£30.04	£31.01	£31.98	£32.94
0.3	£27.59	£28.68	£29.77	£30.86	£31.94	£33.03	£34.12
0.2	£28.04	£29.25	£30.46	£31.67	£32.88	£34.09	£35.30
0.1	£28.49	£29.82	£31.15	£32.48	£33.81	£35.14	£36.47

Cells shaded red indicate the use of FibroScan in primary care to be cost incurring, when compared with use of FibroScan in secondary or specialist care.

The EAC completed a number of scenario analyses, Table 25. Although the clinical experts reported that a behavioural intervention would be likely to be given at the FibroScan appointment, the EAC considered scenarios in which this was given as a separate GP appointment, and as a separate appointment in the same setting as the FibroScan test. As the available clinical evidence is heterogeneous in terms of population, and thresholds used to guide referrals, the EAC also varied proportions being referred to hepatology, for behavioural interventions, or for no further management. For the base case referral proportions only, the EAC also considered that, in secondary care, the follow up for behavioural intervention may be given by a telephone call.

The clinical experts considered that the test failures for FibroScan should be equivalent, regardless of the setting. However, the EAC modelled two scenarios in which test failure varied by setting. The first considered the proportion of failed tests to be 5% in both arms, which included only the unreliable results from Harman *et al*. (2018), and not those who could not be scanned. The second scenario accounted for the possibility of an XL+ probe not being available in primary care, perhaps due to loss or damage, and set failures only in primary care to 7%.

The EAC also considered the impact of FibroScan in primary care being carried out by a community nurse, instead of a practice nurse, and considered the impact of costing missed appointments as nurse time only in both settings, omitting the cost of FibroScan.

To address the possibility that the weighted average cost of ultrasound elastography at £61.98 is more representative, this was also considered as a separate scenario.

Table 25: Scenario analysis using EAC model.

Scenario	Updated values	Cost per patient (primary)	Cost per patient (secondary)	Cost difference
Base-case Behavioural therapy: £0 (assumed within measurement visit)	N/A	£80.57	£51.21	£29.36
Cost of additional GP appointment added to patients receiving behavioural intervention	Behavioural therapy: £39.23	£86.20	£54.97	£31.23
Cost of additional appointment (GP for primary care, outpatients in secondary care) added to patients receiving behavioural intervention	Behavioural therapy: primary care £39.23, Secondary care £164.75	£86.20	£66.99	£19.21

Scenario	Updated values	Cost per patient (primary)	Cost per patient (secondary)	Cost difference
Referral proportions (actual) from Chalmers *et al.* (2020)	Hepatology referral: 108/962 Behavioural intervention: 114/962 No intervention: 740/962	£89.79	£56.09	£33.70
Referral proportions from El-Gohary *et al.* (2018) based on liver stiffness: - Hepatology: ≥13 kPa - Behavioural: 8-12.9 kPa - No intervention: liver warning (6-8 kPa) and no fibrosis (<6 kPa)	Hepatology referral: 44/910 Behavioural intervention: 141/910 No intervention: 725/910	£78.67	£50.21	£28.46
Referral proportions from El-Gohary *et al.* (2018) based on liver stiffness: - Hepatology: ≥13 kPa - Behavioural: progressive 8-12.9 kPa & liver warning (6-8 kPa) - No intervention: no fibrosis (<6 kPa)	Hepatology referral: 44/910 Behavioural intervention: 361/910 No intervention: 505/910	£78.67	£50.21	£21.46
Referral proportions from Matthews *et al.* (2019): - Hepatology: ≥12.5 kPa - Behavioural: ≥8 kPa & < 12.5 kPa - No intervention: liver warning (≥7.1 kPa & <8 kPa) with no intervention (<7.1 kPa)	Hepatology referral: 5/76 Behavioural intervention: 7/76 No intervention: 64/76	£81.70	£51.82	£29.88
Referral proportions from Matthews *et al.* (2019): - Hepatology: ≥12.5 kPa - Behavioural: ≥8 kPa & < 12.5 kPa and liver warning (≥7.1 kPa & <8 kPa)	Hepatology referral: 5/76 Behavioural intervention: 15/76 No intervention: 56/76	£81.70	£51.82	£29.88

Scenario	Updated values	Cost per patient (primary)	Cost per patient (secondary)	Cost difference
- No intervention: no intervention (<7.1 kPa)				
Referral proportions from Roberts *et al.* (2015): - Hepatology: 12-20kPa and >20 kPa - Behavioural: 8-12 kPa - No intervention: <8 kPa	Hepatology referral: 17/182 Behavioural intervention: 19/182 No intervention: 146/182	£86.51	£54.36	£32.15
Decreasing failuresin both arms	Test failure rate of 5% in both arms (α=44, β=855)	£79.98	£50.79	£29.19
Decreasing failure rate in secondary care only	Test failure proportion of 5% in secondary care (α=44, β=855), 7% in primary care (α=64, β=855)	£80.57	£50.86	£29.71
Cost of Band 4 community nurse using FibroScan in primary care, instead of practice nurse	£30.00 per hour	£78.57	£51.21	£24.36
Behavioural intervention in secondary care arm delivered by phone call	Behavioural therapy (secondary care): £89.52	£84.20	£59.79	£24.41
FibroScan cost in secondary care increased to weighted average of all TEs in outpatient setting	FibroScan (secondary care): £61.98	£81.70	£70.02	£11.68
Missed appointment costed as staff time only	Cost of missed appointment: £9.50 (primary care); £12.50 (secondary care)	£73.98	£38.64	£35.34
Abbreviations: TE, transient elastography				

In addition to the scenarios presented in Table 25, the EAC modelled the same sets of referral proportions from different studies, whilst also varying the delivery of behavioural interventions to include their delivery in a separate appointment, either with their GP in all cases, or in the same setting as FibroScan. None of these scenarios were found to be cost saving, and the results have therefore been omitted from Table 25. The EAC considers that the number of referrals for behavioural intervention that would be needed to result in a cost saving, to be unlikely to be realised in practice. These would also need to be delivered in a separate appointment, likely in the same setting as the FibroScan test, which the EAC also considers unlikely, based on clinical expert opinion (EAC Correspondence Log, 2021). The EAC notes that the results in Table 25 using proportions from the same studies, result in the same costs, because the same proportions are referred to hepatology, and behavioural interventions, although in different proportions, are assumed to be be delivered at the same appointment as FibroScan, and therefore incur no additional cost.

Threshold analysis

The EAC considered threshold analysis, in which the cost per FibroScan in primary care was varied, to identify the cost per scan at which its use in primary care became cost neutral. The results of this are shown in Table 26, and the EAC found the threshold below which the use of FibroScan in primary care becomes cost saving is £28.50.

Table 26: Threshold analysis of FibroScan in primary care using EAC model

Cost of FibroScan in primary care	Cost per patient in primary care	Cost per patient in secondary care	Cost difference
£58.00 (base case)	£80.57	£51.21	£29.36
£40.00	£62.57	£51.21	£11.36
£30.00	£52.57	£51.21	£1.36
£25.00	£47.57	£51.21	-£3.64

9.4 *The EAC's interpretation of the economic evidence*

Four published economic studies were identified as being relevant to the scope, and two of these reported cost savings for the use of FibroScan in primary care (Srivastava *et al*. 2019, Crossan *et al*. 2019). These studies, and Tanajewski *et al*. (2018) were from the perspective of the NHS in the UK or England. However, Tanajewski *et al*. (2018) found the use of FibroScan outside of secondary or specialist care likely to be cost neutral. This is likely due to the use of a more broad "at risk" population, compared with the population modelled by Srivastava *et al*. (2019) and Crossan *et al*. (2019), who were known to have NAFLD.

The Company's economic model, based on a decision tree, estimated that use of FibroScan outside a hospital setting would lead to a saving of £41.44 per patient compared with standard care (£139.65 outside hospital versus £180.71 in hospital; 95% CI of saving £12.66 to £71.44). The Company model was applicable to the decision problem, although the EAC considered some assumptions to be inappropriate and after seeking expert opinion, likely not to be in line with current NHS practice. Primarily, the Company had assumed that a failed FibroScan in either setting would not be investigated further. The clinical experts disagreed with this and judged that a further test for fibrosis, or referral to secondary care, should be sought (EAC Correspondence Log, 2021). The clinical experts also considered that for those patients requiring a behavioural intervention, in their experience, this either would be delivered at the same appointment as FibroScan, or in ideal circumstances, should be (EAC Correspondence Log, 2021). This differed from the Company model in that it was assumed that all patients who needed a behavioural intervention were referred back to their GP to receive this. The EAC replicated the Company's model, but identified that the Company had twice included the time required for hospital-based healthcare professionals to perform and interpret scans (once via a micro-costing and once via a bundled tariff cost). The EAC considered that the model was therefore not generalisable to UK NHS use.

The EAC base case addressed these issues in the Company model, and found the use of FibroScan in primary care, compared with the use of FibroScan in secondary or specialist care, to be cost incurring by £29.36 per patient. This result was consistent with Tanajewski *et al*. (2017) who also reported a point estimate for their risk stratification pathway that was cost incurring, when not considering utility. The point estimate of the EAC's base case was consistent with the result of PSA which found the mean cost difference between arms to be £29.35 (95% CI £29.23 to £29.49), and found none of the 1,000 simulations to be cost saving. The confidence interval for PSA was narrow because the EAC found little direct evidence to inform meaningful choices for uncertainty parameters for most model variables. Both one way and two way DSA were also used, which, again, found the use of FibroScan in primary care to be cost incurring. Multiple scenarios were also modelled, in which the proportions having each outcome (hepatology referral, behavioural intervention, and no further management) were varied according to the published literature, and in which it was assumed that those having a behavioural intervention received this at a separate appointment, either with their GP, or in the same setting as FibroScan. Another scenario varied the test failures using published data from Harman *et al*. (2018), from 7% in both arms in the base case, to 5% in both arms, and to 5% in secondary care and 7% in primary care, to account for the possibility of an XL+ probe being unavailable in primary care for those patients who needed it. The cost of FibroScan in primary care was also varied, assuming a community nurse performed the scan, instead of a practice nurse, and the cost of missed appointments were also varied in both arms, assuming they incurred only wasted nurse time and not the cost of the test. The EAC also considered a weighted average HRG cost of all referrals for transient elastography, of £61.98, as the cost of FibroScan in secondary care. However, it is acknowledged this was reported for relatively few investigations, and for only two centres, which means the £43.93 used in the base case is likely to be more representative. The EAC did not find the use of FibroScan in primary care to be cost saving in any modelled scenario, and considers that a large incremental number of referrals for behavioural intervention would be needed, and that these would need to be delivered in the same setting as the

FibroScan test, to change the direction of results. Based on expert opinion, the EAC considers this unlikely to be plausible in NHS practice (EAC Correspondence Log, 2021). The EAC performed threshold analysis on the cost of FibroScan in primary care, and found that, for the base case, the approximate cost per scan below which FibroScan would become cost saving is £28.50.

As stated in the clinical evidence section, the clinical experts advised that approximately one third of FibroScan devices currently used in primary or community care are older models that cannot be upgraded and cannot perform CAP measurement. However, the Company has shared a “pay per scan” model (with minimum 36 month contract, and minimum 25 scans per month) that would support the use of upgraded devices and includes training, installation, service and calibration costs, hardware, M+ and XL+ probes, and CAP (EAC Correspondence Log, 2021). The EAC has calculated that to deliver, using FibroScan in primary care, the 3,688 transient elastography exams delivered in 2019 to 2020 in secondary care, approximately 11 centres performing 25 scans per month each, would be needed. As this number reflects all transient elastography exams, including those using conventional ultrasound instead of FibroScan, and those performed on other organs, even fewer centres may be needed in order to achieve 25 scans per month. Not only will 11 primary care centres offering FibroScan not provide sufficient nationwide coverage to replace FibroScan in secondary care, GPs are potentially likely to use FibroScan in more patients, because it is more readily available to them. Although this is outside of the scope of this assessment, the EAC considers it important to note this possibility, and considers this more likely to be the case in primary care centres that are struggling to meet the requirement of 25 scans per month, as they will be charged for them regardless of whether they are used or not. This may then have implications for detection of liver disease, and onward referral to hepatology, although this has not been modelled.

The EAC notes that neither the Company’s model nor the EAC model consider the following:

- The opportunity costs associated with the current service model of delivering FibroScan in secondary care;
- Efficiency gains and improved service resilience arising from delivering FibroScan tests in a community diagnostic hub setting (either via a pay-per-use model or a capital purchase model);
- Increased utility associated with referring more people to lifestyle intervention programmes.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The Company identified seven papers, of which the EAC considered three out of scope. An independent search by the EAC identified an additional 15 papers. A total of nine peer-reviewed publications (one RCT, five cross-sectional, two cohort and one qualitative study) and ten available in abstract form only were included in the EAC assessment.

There is wide variation in the referral criteria used in current NHS practice for transient elastography measurement in secondary care. No evidence was identified which directly compared the use of FibroScan in primary or community care against its use in secondary or specialist care, in line with the final scope. However, clinical experts advised that attendance of FibroScan assessment in primary or community settings are higher than that of hospital setting. Test failure and unreliable test results from transient elastography measurements were reported in the literature, however this may be related to device/probe availability, limited user experience, or as a direct consequence of patient habitus (the latter also resulting in test failure in hospital setting).

No diagnostic accuracy studies were identified. The clinical experts considered that false negative results may provide false reassurance of lifestyle choices to patients and discourage changing to healthier lifestyle choices. However, at-risk patients would undergo regular review, and because disease progression is slow the patient impact of false negative results from FibroScan used in primary care are low. Unnecessary biopsy may be a consequence of a false positive result, however other investigations are likely to be carried out in secondary care before proceeding to liver biopsy rather than basing a decision on transient elastography results from primary care alone. The experts agreed that the lifestyle interventions recommended if a patient received a false positive result (to support weight loss or reduce drinking) are unlikely to cause harm through inappropriate treatment.

Variability in FibroScan measurements of +/-5 kPa has been reported in two papers. This degree of variability may influence clinical decisions when

applying thresholds to FibroScan outcome (for example thresholds of 6 kPa, 8, 12 and 15 kPa have been applied in the literature). No adverse events associated with FibroScan were identified.

10.2 Conclusions from the economic evidence

Four published economic studies were relevant to the scope, with three from the perspective of the NHS in the UK or England. Two reported cost savings for the use of FibroScan in primary care (Srivastava *et al*. 2019, Crossan *et al*. 2019), and one (Tanajewski *et al*. 2018) found the use of FibroScan outside of secondary or specialist care likely to be cost neutral.

The generalisability of the Company model to UK NHS practice was limited by two assumptions: that a failed FibroScan in either setting would not be investigated further; and that all patients who needed a behavioural intervention would be referred back to their GP to receive this. The Company's decision tree estimated that use of FibroScan in primary care would save £41.44 per patient compared with its use in secondary care (£139.65 versus £180.71; 95% CI of saving £12.66 to £71.44). However, the model included staff time to perform and interpret FibroScan in secondary care, when this was included in the HRG code assumed by the Company as the cost of FibroScan alone.

The EAC base case found the use of FibroScan in primary care, to be cost incurring by £29.36 per patient. Little direct evidence was available to inform uncertainty parameters for most model variables in PSA, but uncertainies were considered in univariate sensitivity or scenario analyses. The EAC did not find the use of FibroScan in primary care to be cost saving in any modelled scenario, and found on threshold analysis using the base case, that the approximate cost per scan below which FibroScan would become cost saving is £28.50.

The Company has shared a "pay per scan" model (with minimum 25 scans per month for minimum contract length of 36 months). Given the relatively low number of transient elastography exams (3,688 in 2019/20) delivered in secondary care, the EAC considers the low number of centres needed to

reach 25 scans per month, unlikely to provide sufficient nationwide coverage to replace FibroScan in secondary care. GPs are also potentially likely to use FibroScan in more patients, because it is more readily available, which may impact on detection of liver disease, and onward referral to hepatology. The EAC considers that although performing the scan outside a hospital setting may be marginally cost incurring, there may be wider economic and patient benefit, particularly if provided as part of an integrated liver assessment pathway with well-defined referral criteria.

11 Summary of the combined clinical and economic sections

The EAC has identified no direct comparative evidence for the relative clinical effectiveness of FibroScan between the two settings. No adverse events were identified. The EAC found that performing the scan outside a hospital setting may be marginally cost incurring on a per-patient basis. Given the Company's "cost per scan" model, implementation in diagnostic hubs may be appropriate, although the minimum 25 scans per month may be difficult to achieve in terms of both patient convenience, and not broadening the referral criteria in a way that overwhelms hepatology services. However, the EAC considers that, provided clinical equivalence is demonstrated, there may be wider economic and patient benefit associated with providing FibroScan outside a hospital setting, particularly if provided as part of an integrated liver assessment pathway with well-defined referral criteria.

12 Implications for research

There are no diagnostic accuracy studies which directly compare the use of FibroScan in non-hospital setting (with GP practice nurses/technicians) with

measurements obtained in a hospital setting (by secondary care healthcare professionals).

Test-retest reliability from published evidence has reported limits of agreement varying up to +/-5 kPa; this may impact clinical interpretation and decision making of referral pathway when thresholds of 6 kPa, 8 kPa, 12 kPa, 15 kPa are set (in line with the published literature).

A study in which each member of a cohort of eligible patients was measured both in one or more primary care locations, and in secondary care (with each setting blinded to the results of the other) would directly address the decision problem (that is whether there is an effect size associated with the setting). By using the principles of efficient experimental design, a similar study approach could also assess the variance associated with test-retest reliability and the effect of other relevant factors, such as operator experience.

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14 Appendices

Appendix A: Clinical literature search

Appendix A1: PRESS checklist for search strategy peer review

Question	Y/N	Notes
Translation of the research question		
Does the search strategy match the research question/PICO?	Yes	
Are the search concepts clear?	Yes	FibroScan and liver and primary care
Are there too many or too few PICO elements included?	Okay	It would also have been appropriate to include UK setting
Are the search concepts too narrow or too broad?	Okay	
Does the search retrieve too many or too few records? (Please show number of hits per line.)	Too few	The Company ran two versions of the search – with and without the term 'primary care'. There were too few records when they included primary care, but that was due to lack of synonyms for that concept, rather than it being inappropriate to include.
Are unconventional or complex strategies explained?	N/A	
Boolean and proximity operators (these vary based on search service)		
Are Boolean or proximity operators used correctly?	Yes	
Is the use of nesting with brackets appropriate and effective for the search?	Yes	
If NOT is used, is this likely to result in any unintended exclusions?	N/A	
Could precision be improved by using proximity operators (eg, adjacent, near, within) or phrase searching instead of AND?	No	
Is the width of proximity operators suitable (eg, might adj5 pick up more variants than adj2)?	N/A	
Subject headings (database specific)		
Are the subject headings relevant?	Yes	
Are any relevant subject headings missing; for example, previous index terms?	Yes	For primary care, a wide range of subject headings could have been used but were not – including 'Primary Health Care' itself.

		Relevant subject headings pertaining to liver were also not used (e.g. 'Liver Cirrhosis'). However, the majority of the records that such subject terms would have retrieved were retrieved anyway by 'liver' being searched across 'all fields'
Are any subject headings too broad or too narrow?	No	
Are subject headings exploded where necessary and vice versa?	Yes	Liver (the only heading used) is not exploded, but its narrower terms aren't that relevant
Are major headings ("starring" or restrict to focus) used? If so, is there adequate justification?	N/A	
Are subheadings missing?	N/A	
Are subheadings attached to subject headings? (Floating subheadings may be preferred.)	N/A	
Are floating subheadings relevant and used appropriately?	N/A	
Are both subject headings and terms in free text (see the following) used for each concept?	No	'Primary care' is searched in title and abstract fields only, not as a subject heading
Text word searching (free text)		
Does the search include all spelling variants in free text (eg, UK vs. US spelling)?	Yes	
Does the search include all synonyms or antonyms (eg, opposites)?	No	There are many additional options for primary care
Does the search capture relevant truncation (ie, is truncation at the correct place)?	N/A	
Is the truncation too broad or too narrow?	N/A	
Are acronyms or abbreviations used appropriately? Do they capture irrelevant material? Are the full terms also included?	N/A	
Are the keywords specific enough or too broad? Are too many or too few keywords used? Are stop words used?	No	More keywords are required
Have the appropriate fields been searched; for example, is the choice of the text word fields (.tw.) or all fields (.af.) appropriate? Are there any other fields to be included or excluded (database specific)?	No	Title and abstract fields are fine, but other fields (including subject heading, device name, keywords, etc) may have been useful to use too

Should any long strings be broken into several shorter search statements?	No	
Spelling, syntax, and line numbers		
Are there any spelling errors?	No	
Are there any errors in system syntax; for example, the use of a truncation symbol from a different search interface?	No	
Are there incorrect line combinations or orphan lines (i.e., lines that are not referred to in the final summation that could indicate an error in an AND or OR statement)?	No	Several terms are rendered superfluous by others – all the liver terms bar liver[All Fields], and "Vibration Controlled Transient Elastography"[Tiab]
Limits and filters		
Are all limits and filters used appropriately and are they relevant given the research question?	Yes	Only a date limit was used (2004-present). This is around the time of the first use of FibroScan so seems relevant. However, FibroScan was first used in 2003, so 2003-present may have been more appropriate.
Are all limits and filters used appropriately and are they relevant for the database?	Yes	
Are any potentially helpful limits or filters missing? Are the limits or filters too broad or too narrow? Can any limits or filters be added or taken away?	No	The date limit could have been 2003-present. No additional limits essential.
Are sources cited for the filters used?	N/A	

Appendix A2: Literature search conducted by EAC

Results from each source

Database name (and platform, where applicable)	Years/dates covered by the search (where applicable)	Number of records retrieved
Ovid MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations and Daily	1 January 2003 to 29 September 2021	69
Embase (on Ovid)	1 January 2003 to 29 September 2021	283
CINAHL (EBSCO)	1 January 2003 to 29 September 2021	94
Cochrane Library (via Wiley) - Cochrane Database of Systematic Reviews	All available to 29 September 2021	2
Cochrane Library (via Wiley) - CENTRAL	All available to 29 September 2021	11
INAHTA	All available to 29 September 2021	2
Clinicaltrials.gov	All available to 29 September 2021	4
WHO ICTRP	All available to 29 September 2021	11
IDEAS/RePEc	All available to 29 September 2021	19
NHSEED	All available to 29 September 2021	3
Total number of records retrieved from all sources		498
Total number of records after de-duplication		410

Source: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations and Daily <1946 to September 29, 2021>

Interface/URL: OvidSP
Database coverage dates: 1946 to present
Search date: 30/9/2021
Retrieved records: 69

1	((transient adj6 elastograph$) and (hepat$ or steato$ or cirrho$ or liver$)).mp.	2674

2	(fibroscan$ or echosens$ or fibro-scan$ or fs402 or fs502 or fs230 or fs430 or fs530 or fs630 or vcte$).mp.	1520
3	liver stiffness measurement$.mp.	1337
4	(controlled attenuation parameter$ and (hepat$ or steato$ or cirrho$ or liver$)).mp.	577
5	1 or 2 or 3 or 4	3954
6	General Practitioners/	8957
7	physicians, family/ or physicians, primary care/	20594
8	general practice/ or family practice/	76534
9	exp Primary Health Care/	174432
10	exp Community Health Services/	317297
11	Ambulatory Care/	44929
12	exp Allied Health Personnel/	51616
13	exp nurses/ or nursing staff/	112434
14	(general practi$ or family practi$ or family physician$ or primary health$ or (primary adj4 (care or screen$)) or (community adj5 (treat$ or care$ or screen$ or intervention$)) or check-up$ or checkup$ or gp or gps or ((community or prevent$) adj3 service$) or outreach).mp,in.	586520
15	(radiologist$ or radiographer$ or sonographer$ or ultrasonographer$ or liver nurse$ or specialist nurse$).mp.	60970
16	(earl$ adj4 (diagnos$ or identif$ or detect$ or screen$)).mp.	323959
17	(low$ adj3 (level$ or value$) adj3 (fat$ or stiff$)).mp.	2426
18	(routine$ adj4 (test$ or practi$ or screen$)).mp.	80418
19	referral.mp.	159729
20	or/6-19	1586576
21	5 and 20	481
22	exp United Kingdom/	379042
23	(national health service* or nhs*).ti,ab,in.	228628
24	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	41924
25	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	2227726
26	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or	1549363

	"chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	
27	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	61691
28	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	228878
29	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	29323
30	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp united kingdom/ or europe/)	3084766
31	(or/22-29) not 30 [UK FILTER FROM https://onlinelibrary.wiley.com/doi/full/10.1111/hir.12252]	2658088
32	21 and 31	71
33	limit 32 to (editorial or letter)	1
34	32 not 33	70
35	limit 34 to yr="2003 -Current"	69

36	limit 35 to english language	69

Source: Ovid Embase <1974 to 2021 September 29>

Interface/URL: OvidSP
Database coverage dates: 1974 to present
Search date: 30/9/2021
Retrieved records: 283

1	((transient adj6 elastograph$) and (hepat$ or steato$ or cirrho$ or liver$)).mp.	7385
2	(fibroscan$ or echosens$ or fibro-scan$ or fs402 or fs502 or fs230 or fs430 or fs530 or fs630 or vcte$).mp.	6637
3	liver stiffness measurement$.mp.	3207
4	(controlled attenuation parameter$ and (hepat$ or steato$ or cirrho$ or liver$)).mp.	1429
5	1 or 2 or 3 or 4	11798
6	general practitioner/	106035
7	general practice/	80155
8	primary medical care/	114435
9	exp community care/	121480
10	(general practi$ or family practi$ or family physician$ or primary health$ or (primary adj4 (care or screen$)) or (community adj5 (treat$ or care$ or screen$ or intervention$)) or check-up$ or checkup$ or gp or gps or ((community or prevent$) adj3 service$) or outreach).mp,in.	836450
11	ambulatory care/ or ambulatory care nursing/ or ambulatory monitoring/ or ambulatory care.mp.	55398
12	exp paramedical personnel/	533538
13	(radiologist* or radiographer* or sonographer* or ultrasonographer* or liver nurse* or specialist nurse*).mp.	107953
14	(earl$ adj4 (diagnos$ or identif$ or detect$ or screen$)).mp.	461864
15	(low$ adj3 (level$ or value$) adj3 (fat$ or stiff$)).mp.	3079
16	(routine$ adj4 (test$ or practi$ or screen$)).mp.	106555
17	referral.mp.	245622
18	or/6-17	2164577
19	5 and 18	1648
20	exp United Kingdom/	434932
21	(national health service* or nhs*).ti,ab,in,ad.	397608
22	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	49552

23	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jx,in,ad.	3382113
24	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in,ad.	2624473
25	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in,ad.	107522
26	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in,ad.	360975
27	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in,ad.	49360

28	(exp "arctic and antarctic"/ or exp oceanic regions/ or exp western hemisphere/ or exp africa/ or exp asia/ or exp "australia and new zealand"/) not (exp united kingdom/ or europe/)	3363737
29	(or/20-27) not 28 [UK FILTER FROM https://onlinelibrary.wiley.com/doi/full/10.1111/hir.12252]	3885058
30	19 and 29	296
31	limit 30 to (editorial or erratum or letter or note or short survey or tombstone)	10
32	30 not 31	286
33	limit 32 to yr="2003 -Current"	284
34	limit 33 to english language	283

Source: CINAHL

Interface/URL: EBSCO
Database coverage dates: 1981 to present
Search date: 30/9/2021
Retrieved records: 94

#	Query	Results
S1	((transient N6 elastograph*) AND (hepat* OR steato* OR cirrho* OR liver*))	579
S2	(fibroscan* OR echosens* OR fibro-scan* OR fs402 OR fs502 OR fs230 OR fs430 OR fs530 OR fs630 OR vcte*)	294
S3	("liver stiffness" W1 measurement*)	305
S4	((("controlled attenuation" W1 parameter*) and (hepat* OR steato* OR cirrho* OR liver*)))	133
S5	S1 OR S2 OR S3 OR S4	912
S6	(MH "Physicians, Family")	21,272
S7	(MH "Family Practice")	25,757
S8	(MH "Community Health Services+")	451,012
S9	(MH "Ambulatory Care")	12,695
S10	(MH "Allied Health Personnel+")	131,556
S11	(MH "Nurses+")	233,310
S12	TX ((general W1 practi*) OR (family W1 practi*) OR (family W1 physician*) OR (primary W1 health*) OR (primary N4 (care OR screen*)) OR (community N5 (treat* OR care* OR screen* or intervention*)) OR check-up* OR checkup* or gp or gps or ((community or prevent*) N3 service*) or outreach)	384,112

S13	((radiologist* OR radiographer* OR sonographer* OR ultrasonographer* OR (liver W1 nurse*) OR (specialist W1 nurse*)))	27,691
S14	((earl* N4 (diagnos* OR identif* OR detect* OR screen*)))	79,587
S15	((low* N3 (level* OR value*) N3 (fat* OR stiff*)))	879
S16	((routine* N4 (test* OR practi* OR screen*)))	24,898
S17	referral	78,163
S18	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	1,208,641
S19	S18 and S5	131
S20	(MH "United Kingdom+")	326,199
S21	TX ((("national health" W1 service*) OR nhs*))	135,116
S22	TX ((english not ((published OR publication* OR translat* OR written OR language* OR speak* OR literature OR citation*) N5 english)))	7,571,944
S23	TX ((bath OR "bath's" OR ((birmingham not alabama*) OR ("birmingham's" not alabama*) OR bradford OR "bradford's" OR brighton OR "brighton's" OR bristol OR "bristol's" OR carlisle* OR "carlisle's" OR (cambridge not (massachusetts* OR boston* OR harvard*)) OR ("cambridge's" not (massachusetts* OR boston* OR harvard*)) OR (canterbury not zealand*) OR ("canterbury's" not zealand*) OR chelmsford OR "chelmsford's" OR chester OR "chester's" OR chichester OR "chichester's" OR coventry OR "coventry's" OR derby OR "derby's" OR (durham not (carolina* OR nc)) OR ("durham's" not (carolina* OR nc)) OR ely OR "ely's" OR exeter OR "exeter's" OR gloucester OR "gloucester's" OR hereford OR "hereford's" OR hull OR "hull's" OR lancaster OR "lancaster's" OR leeds* OR leicester OR "leicester's" OR (lincoln not nebraska*) OR ("lincoln's" not nebraska*) OR (liverpool not (new south wales* OR nsw)) OR ("liverpool's" not (new south wales* OR nsw)) OR ((london not (ontario* OR ont OR toronto*)) OR ("london's" not (ontario* OR ont OR toronto*)) OR manchester OR "manchester's" OR (newcastle not (new south wales* OR nsw)) OR ("newcastle's" not (new south wales* OR nsw)) OR norwich OR "norwich's" OR nottingham OR "nottingham's" OR oxford OR "oxford's" OR peterborough OR "peterborough's" OR plymouth OR "plymouth's" OR portsmouth OR "portsmouth's" OR preston	1,372,741

	OR "preston's" OR ripon OR "ripon's" OR salford OR "salford's" OR salisbury OR "salisbury's" OR sheffield OR "sheffield's" OR southampton OR "southampton's" OR st albans OR stoke OR "stoke's" OR sunderland OR "sunderland's" OR truro OR "truro's" OR wakefield OR "wakefield's" OR wells OR westminster OR "westminster's" OR winchester OR "winchester's" OR wolverhampton OR "wolverhampton's" OR (worcester not (massachusetts* OR boston* OR harvard*)) OR ("worcester's" not (massachusetts* OR boston* OR harvard*)) OR (york not ("new york*" OR ny OR ontario* OR ont OR toronto*)) OR ("york's" not ("new york*" OR ny OR ontario* OR ont OR toronto*)))))))	
S24	TX ((gb OR "g.b." OR britain* OR (british* not "british columbia") OR uk OR "u.k." OR united kingdom* OR (england* not "new england") OR northern ireland* OR northern irish* OR scotland* OR scottish* OR ((wales OR "south wales") not "new south wales") OR welsh*))	2,073,572
S25	TX ((bangor OR "bangor's" OR cardiff OR "cardiff's" OR newport OR "newport's" OR st asaph OR "st asaph's" OR st davids OR swansea OR "swansea's"))	24,171
S26	TX ((aberdeen OR "aberdeen's" OR dundee OR "dundee's" OR edinburgh OR "edinburgh's" OR glasgow OR "glasgow's" OR inverness OR (perth not australia*) OR ("perth's" not australia*) OR stirling OR "stirling's"))	74,652
S27	TX ((armagh OR "armagh's" OR belfast OR "belfast's" OR lisburn OR "lisburn's" OR londonderry OR "londonderry's" OR derry OR "derry's" OR newry OR "newry's"))	10,447
S28	(MH "Africa+") OR (MH "America+") OR (MH "Antarctic Regions") OR (MH "Arctic Regions") OR (MH "Asia+") OR (MH "Atlantic Islands+") OR (MH "Australia+") OR (MH "Indian Ocean Islands+") OR (MH "Pacific Islands+")	1,426,885
S29	(MH "Europe") OR (MH "United Kingdom+")	355,684
S30	(S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27) NOT (S28 NOT S29)	6,244,856
S31	S30 AND S19	95
S32	S31 [Limiters - Published Date: 20030101-; English Language]	94

Source: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)

Interface/URL: Cochrane Library via Wiley
Database coverage dates: 1995 to present
Search date: 30/9/2021
Retrieved records: CDSR: 2, CENTRAL: 11

ID	Search	Hits
#1	(((transient NEAR/6 elastograph*) AND (hepat* OR steato* OR cirrho* OR liver*))):ti,ab,kw	275
#2	((fibroscan* OR echosens* OR fibro-scan* OR fs402 OR fs502 OR fs230 OR fs430 OR fs530 OR fs630 OR vcte*)):ti,ab,kw	526
#3	("liver stiffness" NEXT measurement*):ti,ab,kw	130
#4	((("controlled attenuation" NEXT parameter*) and (hepat* OR steato* OR cirrho* OR liver*))):ti,ab,kw	134
#5	#1 or #2 or #3 or #4	764
#6	MeSH descriptor: [General Practitioners] this term only	304
#7	MeSH descriptor: [Physicians, Family] this term only	457
#8	MeSH descriptor: [Physicians, Primary Care] this term only	164
#9	MeSH descriptor: [General Practice] explode all trees	2472
#10	MeSH descriptor: [Primary Health Care] explode all trees	7875
#11	MeSH descriptor: [Community Health Services] explode all trees	14573
#12	MeSH descriptor: [Ambulatory Care] this term only	3259
#13	MeSH descriptor: [Allied Health Personnel] explode all trees	1250
#14	MeSH descriptor: [Nurses] explode all trees	1278
#15	MeSH descriptor: [Nursing Staff] this term only	208
#16	(((general NEXT practi*) OR (family NEXT practi*) OR (family NEXT physician*) OR (primary NEXT health*) OR (primary NEAR/4 (care or screen*)) OR (community NEAR/5 (treat* OR care* OR screen* OR intervention*)) OR check-up* OR checkup* OR gp OR gps OR ((community OR prevent*) NEXT/3 service*) OR outreach))	71011
#17	((radiologist* OR radiographer* OR sonographer* OR ultrasonographer* OR (liver NEXT nurse*) OR (specialist NEXT nurse*))):ti,ab,kw	4016
#18	((earl* NEAR/4 (diagnos* OR identif* OR detect* OR screen*))):ti,ab,kw	11789
#19	((low* NEAR/3 (level* OR value*) NEAR/3 (fat* OR stiff*))):ti,ab,kw	380
#20	((routine* NEAR/4 (test* OR practi* OR screen*))):ti,ab,kw	7586
#21	(referral):ti,ab,kw	12600

#22	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	114154
#23	#5 AND #22	62
#24	MeSH descriptor: [United Kingdom] explode all trees	6674
#25	((("national health" NEXT service*) OR nhs*))	15785
#26	((english not ((published OR publication* OR translat* OR written OR language* OR speak* OR literature OR citation*) NEAR/5 english))):ti,ab,kw	3376
#27	((bath OR "bath's" OR ((birmingham not alabama*) OR ("birmingham's" not alabama*) OR bradford OR "bradford's" OR brighton OR "brighton's" OR bristol OR "bristol's" OR carlisle* OR "carlisle's" OR (cambridge not (massachusetts* OR boston* OR harvard*)) OR ("cambridge's" not (massachusetts* OR boston* OR harvard*)) OR (canterbury not zealand*) OR ("canterbury's" not zealand*) OR chelmsford OR "chelmsford's" OR chester OR "chester's" OR chichester OR "chichester's" OR coventry OR "coventry's" OR derby OR "derby's" OR (durham not (carolina* OR nc)) OR ("durham's" not (carolina* OR nc)) OR ely OR "ely's" OR exeter OR "exeter's" OR gloucester OR "gloucester's" OR hereford OR "hereford's" OR hull OR "hull's" OR lancaster OR "lancaster's" OR leeds* OR leicester OR "leicester's" OR (lincoln not nebraska*) OR ("lincoln's" not nebraska*) OR (liverpool not (new south wales* OR nsw)) OR ("liverpool's" not (new south wales* OR nsw)) OR ((london not (ontario* OR ont OR toronto*)) OR ("london's" not (ontario* OR ont OR toronto*)) OR manchester OR "manchester's" OR (newcastle not (new south wales* OR nsw)) OR ("newcastle's" not (new south wales* OR nsw)) OR norwich OR "norwich's" OR nottingham OR "nottingham's" OR oxford OR "oxford's" OR peterborough OR "peterborough's" OR plymouth OR "plymouth's" OR portsmouth OR "portsmouth's" OR preston OR "preston's" OR ripon OR "ripon's" OR salford OR "salford's" OR salisbury OR "salisbury's" OR sheffield OR "sheffield's" OR southampton OR "southampton's" OR st albans OR stoke OR "stoke's" OR sunderland OR "sunderland's" OR truro OR "truro's" OR wakefield OR "wakefield's" OR wells OR westminster OR "westminster's" OR winchester OR "winchester's" OR wolverhampton OR "wolverhampton's" OR (worcester not (massachusetts* OR boston* OR harvard*)) OR ("worcester's" not (massachusetts* OR boston* OR harvard*)) OR (york not ("new york*" OR ny OR ontario* OR ont OR toronto*)) OR ("york's" not ("new york*" OR ny OR ontario* OR ont OR toronto*))))))	99511
#28	((gb OR "g.b." OR britain* OR (british* not "british columbia") OR uk OR "u.k." OR united kingdom* OR (england* not	159559

	"new england") OR northern ireland* OR northern irish* OR scotland* OR scottish* OR ((wales OR "south wales") not "new south wales") OR welsh*))	
#29	((bangor OR "bangor's" OR cardiff OR "cardiff's" OR newport OR "newport's" OR st asaph OR "st asaph's" OR st davids OR swansea OR "swansea's"))	2515
#30	((aberdeen OR "aberdeen's" OR dundee OR "dundee's" OR edinburgh OR "edinburgh's" OR glasgow OR "glasgow's" OR inverness OR (perth not australia*) OR ("perth's" not australia*) OR stirling OR "stirling's"))	18479
#31	((armagh OR "armagh's" OR belfast OR "belfast's" OR lisburn OR "lisburn's" OR londonderry OR "londonderry's" OR derry OR "derry's" OR newry OR "newry's"))	1778
#32	#24 or #25 or #26 or #27 or #28 or #29 or #30 or #31	193408
#33	#23 AND #32	13

Source: INAHTA

Interface/URL: https://database.inahta.org/
Search date: 30/9/2021
Retrieved records: 2(fibroscan OR echosens OR "fibro scan" OR fs402 OR fs502 OR fs230 OR fs430 OR fs530 OR fs630 OR vcte OR fibroscanr OR fibroscantm OR echosensr OR echosenstm OR "fibro scanr" OR "fibro scantm" OR (transient AND elastograph) OR (transient AND elastography)) AND ("united kingdom" OR uk OR britain OR england OR scotland OR wales OR "northern ireland")[Country]

link

Source: Clinicaltrials.gov

Interface/URL: https://clinicaltrials.gov/
Search date: 30/9/2021
Retrieved records: 4

fibroscan OR echosens OR "fibro scan" OR fs402 OR fs502 OR fs230 OR fs430 OR fs530 OR fs630 OR vcte OR fibroscanr OR fibroscantm OR echosensr OR echosenstm OR (transient AND elastograph) OR (transient AND elastography) | United Kingdom

link

Source: WHO International Clinical Trials Platform (ICTRP)

Interface/URL: https://trialsearch.who.int/
Search date: 30/9/2021
Retrieved records: 191; after manual removal of non-UK location results: 11

All fields:

(fibroscan OR echosens OR "fibro scan" OR fs402 OR fs502 OR fs230 OR fs430 OR fs530 OR fs630 OR vcte OR fibroscanr OR fibroscantm OR echosensr OR echosenstm OR "fibro scanr" OR "fibro scantm" OR (transient AND elastograph) OR (transient AND elastography))

Source: IDEAS/RePEc

Interface/URL: https://ideas.repec.org/
Search date: 30/9/2021
Retrieved records: 19

(fibroscan | echosens | fibro-scan | fs402 | fs502 | fs230 | fs430 | fs530 | fs630 | vcte | fibroscanr | fibroscantm | echosensr | echosenstm | (transient + elastograph) | (transient + elastography))

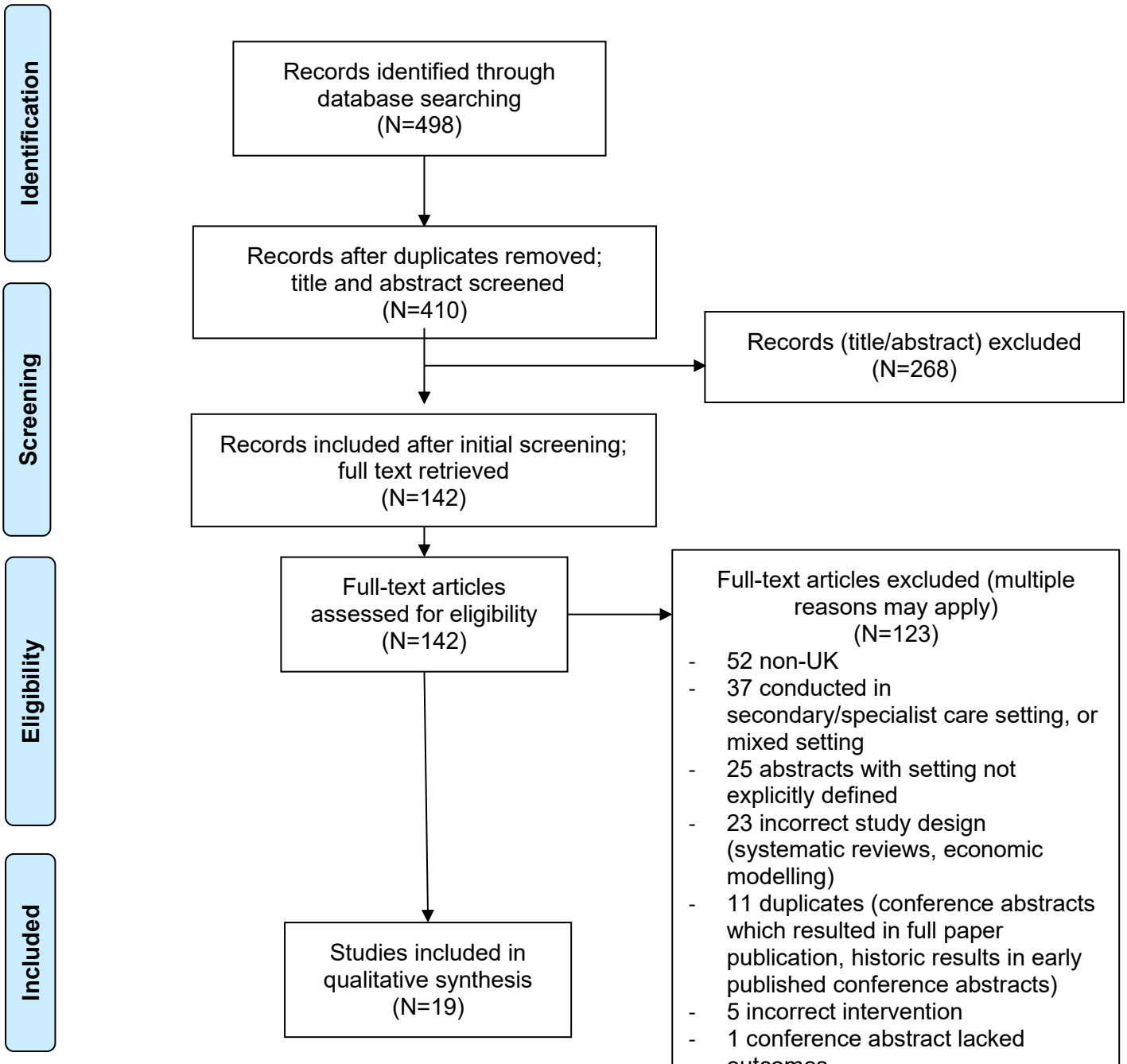
Source: NHS Economic Evaluation Database (NHSEED)

Interface/URL: CRD database
Search date: 30/9/2021
Retrieved records: 19

(fibroscan OR echosens OR "fibro scan" OR fs402 OR fs502 OR fs230 OR fs430 OR fs530 OR fs630 OR vcte OR fibroscanr OR fibroscantm OR echosensr OR echosenstm OR (transient AND elastograph) OR (transient AND elastography))

Appendix A3: PRISMA diagram illustrating EAC literature search

[From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097]



Appendix B: Critical appraisal of clinical evidence

Appendix B1: RCTs (Cochrane Collaboration's tool for assessing risk of bias)

El-Gohary *et al.* 2018, n=26,838 eligible in intervention arm, and n=26,236 eligible in control arm, however only 910 attended liver clinic and had FibroScan measurement taken).
First reviewer: KK; Second review: RO

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	Allocation of GP practices was carried out via simple cluster randomisation at a 1:1 ratio without matching (method of randomised sequence not described more fully).	Unclear
	Allocation concealment	Intervention practices included 3 subgroups, all of which required GP or practice nurse case finding. Intervention practices had higher proportion of males (55.5% vs 50.8%), lower median age (44 vs. 50 years), lower proportion of diabetes (3.0% vs. 5.8%) and higher alcohol misuse (4.2% vs. 3.0%), although this was explained by the local demographic. Authors note that prevalence of pre-existing liver disease was the same across intervention and control groups.	High risk
Performance bias	Blinding of participants and personnel*	Cannot blind patients, GPs, or practice nurses to invitations to liver health check clinic (where transient elastography and blood tests were carried out).	High risk (but unavoidable)
Detection bias	Blinding of outcome assessment*	Only patients with evidence of liver fibrosis (probable cirrhosis, progressive fibrosis, liver warning) were assessed in a virtual combined clinic by a GP and consultant hepatologist (clinical, fibrosis and liver aetiology blood tests were examined). Where required further additional tests suggested to GP.	High risk
Attrition bias	Incomplete outcome data*	Only those attending clinic included (n=910)	Low risk
Reporting bias	Selective reporting	In 2492/7183 notes were not examined (no reason provided). Baseline characteristics only	High risk

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
		reported for those aged >25 years (Table 1); authors state that one practice had large university student population. No reported tabulation of FibroScan scores (<6, 6 to 8, 8 to 12.9, ≥13) and final diagnosis (no fibrosis, liver warning, progressive fibrosis, probable cirrhosis) as determined by FibroScan, clinical and liver aetiology data. Author acknowledge no liver biopsy conducted (pragmatic design), therefore no histological confirmation; however patients with evidence of liver fibrosis reviewed by hepatologist and further investigation arranged if required. No follow-up of patients; cannot state whether early diagnosis translates into better outcomes.	
Other bias	Anything else, ideally pre-specified.	Funding: British Liver Trust, NIHR. Funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. Conflicts declared: advisory roles to Public Health England, professional societies. Consultancy work and travelling expenses from pharmaceutical companies. Numbers of patients in subgroups and referrals do not match data flow diagram. Potential spectrum bias as those who participated may not represent all those eligible: Pathway 1: 715 referred by GP, 627 invited, and 272 took part. Pathway 2: 4397 patients at risk, 1235 invited, and 465 took part. Pathway 3: 2071/9510 responded to AUDIT mailshot, 220 invited, 173 took part.	High risk

*Assessments should be made for each main outcome or class of outcomes.

Appendix B2: Observational studies (STROBE: cross-sectional)

Harman *et al.* (2018); n=919 patients

First reviewer: KK; Second review: RO

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	Title: Obesity and type 2 diabetes are important risk factors underlying previously undiagnosed cirrhosis in general practice: a cross-sectional study using transient elastography
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Aims, methods, results and conclusions in abstract. setting described in methods
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	Increase in cirrhosis incidence in England between 1998 and 2009, and premature mortality. Increase in obesity is likely to cause increase in non-alcoholic fatty liver disease. Previous study demonstrated transient elastography can detect liver disease in people with hazardous alcohol use and type 2 diabetes.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	Extension of previous study (on type 2 diabetes) additional recruitment to characterise clinically significant liver disease and cirrhosis, and identify risk factors.
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	"This was a cross-sectional study with recruitment from four general medical practices in Nottingham, United Kingdom." ClinicalTrials.gov registration: NCT02037867.
Setting	5	Describe the setting, locations, and relevant dates, including periods	Yes	Locations in Nottingham (2 affluent suburban, 2 predominantly deprived

	Item No	Recommendation	Judgement	Support for judgement
		of recruitment, exposure, follow-up, and data collection		areas). Recruitment between February 2012 and September 2014. Patients identified from electronic record search (SystmOne system).
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes	Adults (≥18 years) with risk factors (hazardous alcohol use, type 2 diabetes, or persistently elevated serum alanine aminotransferase withneither hazardous alcohol use or type 2 diabetes). Patients were excluded if definitive evidence of hepatic fibrosis or cirrhosis from previous investigations, contraindication to transient elastography (pregnancy, indwelling cardiac device), metastatic malignancy, unable to consent due to cognitive impairment, housebound. Patients presenting with symptoms of decompensated liver cirrhosis (e.g. jaundice, variceal bleeding, ascites) were also excluded and triaged straight to urgent hospital-based care rather than being screened using transient elastography in primary care.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	BMI (cut off for probe selection), age, gender, ischaemic heart disease, hypertension, hyperlipidaemia reported in baseline characteristics. Device failure, that is, inability to obtain 10 valid measurements. Unreliable acquisition if result ≥7.1 kPa and IQR/median ratio >0.3. Clinically significant liver disease diagnosed if ≥8.0 kPa. Patients with BMI>35kg/m^2

	Item No	Recommendation	Judgement	Support for judgement
				underwent transient elastography in hospital setting with FibroScan FS502 and XL+ probe (out of scope).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Yes*	One of three nurses conducted transient elastography in general practice setting, plus "electronic primary care records were retrospectively examined to collect recent relevant clinical, anthropometric and laboratory test data"
Bias	9	Describe any efforts to address potential sources of bias	Yes (partially)	Univariate analysis to determine risk factors, however no multi-variate analysis conducted.
Study size	10	Explain how the study size was arrived at	No	Assumed to be total patient throughput of GP practices.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	Categorical data are presented as number (percentage). Continuous data are presented as medians (range),as all were non-normally distributed.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	"Demographic, anthropometric and laboratory test data were compared between patients with and without cirrhosis using the Mann-Whitney test as appropriate. Categorical variables were compared using chi-squared test or Fisher's exact test where appropriate."
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	"To further evaluate the association of clinical and metabolic risk factors with clinically significant liver disease, for those risk factors which were associated with both presence of elevated liver stiffness and cirrhosis we report univariate odds ratios and 95% confidence intervals comparing patients with and without these clinical features

	Item No	Recommendation	Judgement	Support for judgement
				in each of our studied groups."
		(*c*) Explain how missing data were addressed	No	Only missing values of BMI reported in Table 1.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A	Not applicable
		(*e*) Describe any sensitivity analyses	No	None conducted
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	Section 3.1 Study population, and Figure 1.
		(b) Give reasons for non-participation at each stage	Yes	Figure 1
		(c) Consider use of a flow diagram	Yes	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes (partially)	Baseline characteristics of total adult population at suburban and inner city GP patients in Table 1; but not provided for the whole cohort with FibroScan measurements taken.
		(b) Indicate number of participants with missing data for each variable of interest	Yes (partially)	Only BMI has missing data reported in table 1, patients with no transient elastography results or invalid results reported in Figure 1.
Outcome data	15*	Report numbers of outcome events or summary measures	Yes	"Overall, elevated liver stiffness of ≥8 kPa was observed in 230 patients (25.6%)." "During the study, 209 patients with elevated liver stiffness attended and were reviewed in hepatology clinics and 27 of these were newly diagnosed with liver cirrhosis during the study period (3% of valid liver stiffness results)."
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	Yes	Table 2, and odds ratios with 95% CI reported incorporating obesity, metabolic syndrome,

	Item No	Recommendation	Judgement	Support for judgement
		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		elevated ALT reported in Table 5.
		(*b*) Report category boundaries when continuous variables were categorised	Yes (in methods)	Hazardous alcohol use and ALT elevation defined in methods.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	Odds ratios reported throughout.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	Cirrhosis prevalence across subgroups (alcohol, type 2 diabetes and alcohol and diabetes) shown in Figure 2.
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	One of the largest studies evaluating transient elastography in screening populations for liver disease in a community setting with targeted risk factors. "Grouping by risk factor we found that of those screened due to Type 2 diabetes, a history of alcohol misuse or both 3.7%, 2.8% and 7.7% respectively were diagnosed with cirrhosis. When the risk factors were combined this resulted in a greater 'yield' of detecting cirrhosis."
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Only 45% of eligible population underwent transient elastography. Screening attenders were older, higher proportion female, with differing proportion of hazardous alcohol use and Type 2 diabetes than non-attenders. "…it is likely that we have screened the highest risk patients with obesity within the

	Item No	Recommendation	Judgement	Support for judgement
				population, but we will have not detected patients with clinically significant liver disease and obesity alone as a risk factor."
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	Section 4.3 Comparison with other studies, discussing accuracy of transient elastography in stratifying fibrosis stage in secondary care, prevalence of cirrhosis.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	Section 4.4 Implications.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	Declaration of personal interests: None. Declaration of funding interests: NIHR Nottingham BRC, East Midlands AHSN. Study sponsor is University of Nottingham as data custodian, but had no role in design, analysis or interpretation.

*Give information separately for exposed and unexposed groups.

Harman *et al.* (2015); n=378

First reviewer: KK; Second review: RO

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	Title: Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography. Prospective defined in abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Objectives, design, setting (2 primary care practices in Nottingham), participants, interventions, outcome measures, results in abstract. Number of new diagnoses of liver cirrhosis reported.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	Absence of symptoms in early stages of liver disease and poor sensitivity of liver function tests to detect fibrosis results in late diagnosis. Cites a recent study where 50% of patients with cirrhosis were given initial diagnosis after first hospitalisation with decompensation.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	Assess feasibility of pathway integrating non-invasive diagnostic tests and liver specialists in community setting, particularly targeting risk groups. Hypothesis is that this approach would detect a substantial number of undiagnosed cases of chronic liver disease.
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	At the end of the abstract: "The diagnostic algorithm

	Item No	Recommendation	Judgement	Support for judgement
				utilised for this study can be found on clinicaltrials.gov (NCT02037867), and is part of a continuing longitudinal cohort study."
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	Locations in Nottingham (2 suburban general medical practices in the least deprived borough). Recruitment between February 2012 and April 2013 [subset of Harman *et al*. 2018]. Patients identified from electronic record search (SystmOne system) using READ codes.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes	Adults (18 years or older) with risk factors (hazardous alcohol use, type 2 diabetes, or persistently elevated serum alanine aminotransferase with neither hazardous alcohol use or type 2 diabetes). Patients were eligible regardless of previous liver function blood test results. Patients were excluded if definitive evidence of hepatic fibrosis or cirrhosis from previous investigations, contraindication to transient elastography (pregnancy, indwelling cardiac device), unable to consent to investigation or were housebound and could not attend the community practice. Patients with type 2 diabetes were invited opportunistically at their diabetes annual review. Patients with hazardous alcohol use were invited opportunistically during primary care appointments or via letter where they did

	Item No	Recommendation	Judgement	Support for judgement
				not undergo a consultation during the study period. Patients in the raised ALT subgroup were prospectively referred by the investigating GP.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	AST:ALT ratio cut-off of 0.8 was used to rule out hepatic fibrosis. BARD score of at least 2 indicated increased risk of hepatic fibrosis. Patients with a normal simple biomarker test result did not proceed down the diagnostic algorithm. Scan failure, defined as inability to obtain 10 valid measurements in a single patient. Unreliable acquisition if result at least 7.1 kPa and IQR/median ratio greater than 0.3. Clinically significant liver disease diagnosed if result at least 8.0 kPa. Patients with BMI greater than 35kg/m^2 underwent transient elastography in hospital setting with FibroScan
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes (partially)	TE was performed by one of three trained nurses (all performed more than 50 examinations at hospital prior to start of study) using the FibroScan FS402 device. Assume electronic records/lab results (but not explicitly reported in methods).
Bias	9	Describe any efforts to address potential sources of bias	Yes (partially)	Baseline characteristics of those taking part in study compared to those registered at GP (Table 1). Limited univariate analysis described (no multivariate analysis conducted).
Study size	10	Explain how the study size was arrived at	No	Assumed to be total eligible patient

	Item No	Recommendation	Judgement	Support for judgement
				throughput of GP practices.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	Categorical data are presented as number (percentage). Continuous data are presented as mean (SD) for parametric data and median (range) for non-paramteric data. Cut-offs described for elevated ALT, TE and BMI.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	"Anthropometric and biochemical data were compared between patients with normal and elevated liver stiffness—continuous variables were compared using the two sample t test for parametric variables and Mann-Whitney test for non-parametric variables. Categorical variables were compared using χ^2 test, or Fisher's exact test where appropriate."
		(*b*) Describe any methods used to examine subgroups and interactions	No	Not reported.
		(*c*) Explain how missing data were addressed	No	Not reported
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	No	None conducted
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	Study population section: 10,479 adults, 920 invited to study, Figure 1.
		(b) Give reasons for non-participation at each stage	Yes	Study population section, Figure 1.
		(c) Consider use of a flow diagram	Yes	Figure 1

	Item No	Recommendation	Judgement	Support for judgement
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	Baseline characteristics Table 1. Table 2 reports characteristics of subgroups with raised blood biomarker result undergoing TE.
		(b) Indicate number of participants with missing data for each variable of interest	No	Not reported.
Outcome data	15*	Report numbers of outcome events or summary measures	Yes	New observed cirrhosis in 11 patients. Diagnoses using serum score thresholds also reported (APRI, FIB-4).
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No	Not reported
		(*b*) Report category boundaries when continuous variables were categorised	Yes (partially)	TE at least 8kPa for clinically significant liver disease (threshold for cirrhosis undefined).
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	Cross-tabulation of stratification versus ALT results (Table 3). Breakdown of stratification by patient subgroup (Figure 3).
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	First study to stratify patients based on blood biomarkers and TE in UK. Diagnosis of new cases, the majority of which would have been missed using liver function tests. Non-attendance rates <5%.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Could not assess sensitivity of the algorithm, patient uptake of screening (55% of targeted patients) was low. Results likely lower estimate.

	Item No	Recommendation	Judgement	Support for judgement
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	Implications for clinicians and policy makers. Lacks long-term outcomes (to quantify healthcare resource benefit).
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	Only included patients from specific medical practices within a distinct sociodemographic area in UK; attendance and detection may differ in other regions.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	Internal funding for study was provided by the NIHR Nottingham Digestive Diseases Biomedical Research Unit, part of the University of Nottingham and Nottingham University Hospitals NHS Trust. The study sponsor is the University of Nottingham, who are data custodians. The article presents independent research funded by the National Institute for Health Research (NIHR). All authors declare that they are free from other sources of external funding related to this study. Competing interests: None declared.

*Give information separately for exposed and unexposed groups.

Harris *et al.* (2019); n=576 patients

First reviewer: KK; Second review: RO

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	Title: Obesity Is the Most Common Risk Factor for Chronic Liver Disease: Results From a Risk Stratification Pathway Using Transient Elastography Cross-sectional not mentioned in paper however methods are reported as in Harman studies and NCT trial number referenced. "Prospective" is defined.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Intro, methods, results and discussion in abstract. Prospective recruitment from primary care practice with hazardous alcohol use and/or type 2 diabetes and/or obesity. Number with elevated reading, association with risk factors (including multivariate logistic regression) reported.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	Scale of obesity (2.1 billion people in 2013) and risk of liver disease. This study is an extension to previous work with predefined risk factors.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"The aim of this study was to characterise the risk of clinically significant liver disease assessed by TE within subpopulations of a community who were stratified based on their risk factors for obesity and/or type 2 diabetes and/or hazardous alcohol use."
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	The study has been registered on a trials registry website

	Item No	Recommendation	Judgement	Support for judgement
				(NCT02037867). Prospective.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	Single centre (primary care practice) in Leicester. Recruitment between January 2015 and March 2016 (after Harman *et al*. 2015 and Harman *et al.* 2018). Clinical, anthropometric and biochemical data were obtained from the electronic primary care records (SystmOne system), via READ codes.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes	Adults (at least 18 years) with risk factors (hazardous alcohol use, type 2 diabetes, or persistently elevated serum alanine aminotransferase with neither hazardous alcohol use or type 2 diabetes). Patients were excluded if contraindicated to transient elastography (pregnancy, indwelling cardiac device), known diagnosis of chronic liver disease, known malignancy or terminal illness, and inability to consent to investigation or housebound and therefore unable to attend practice.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	Portable FibroScan FS402 used. Threshold of at least 8.0kPa was agreed a priori to define elevated liver stiffness, consistent with clinically significant liver disease (irrespective of probe used). Potentially unreliable acquisition if result fewer than 10 measurements and IQRto median ratio greater than 0.3.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment	Yes	Three experienced operators performed all the TE examinations as per the manufacturer's

	Item No	Recommendation	Judgement	Support for judgement
		(measurement). Describe comparability of assessment methods if there is more than one group		recommendations. All subjects were first examined with the M+ probe, and where this gave an unreliable reading, were rescanned with the XL+ probe.
Bias	9	Describe any efforts to address potential sources of bias	Yes	Univariate and multivariate logistic regression models. Subgroup analysis of risk factors.
Study size	10	Explain how the study size was arrived at	Yes (in discussion)	"To limit selection bias, we were able to identify and invite all eligible patients from a single primary care practice coded to have the relevant lifestyle-related risk factors for chronic liver disease."
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	"Characteristics of the study cohort are presented as numbers (percentage) for categorical data and medians (IQR) for non-normally distributed continuous data."
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	"We used X^2 tests for categorical data and the Wilcoxon signed-rank test for non-normally distributed continuous data. We constructed univariate and multivariate logistic regression models of the associations of an elevated TE reading (≥8.0 kPa), considering associations with and between BMI, age, gender, type 2 diabetes, hazardous alcohol use, being a previous smoker, hypertension, hyperlipidemia, and ischemic heart disease."
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	"Subgroup analyses were completed on those patients who had only obesity as a solitary risk factor for chronic liver disease and on those with and without an elevated

	Item No	Recommendation	Judgement	Support for judgement
				alanine aminotransferase (ALT)."
		(*c*) Explain how missing data were addressed	No	Not reported
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	"The primary care practice had a total adult population of 4,150, of which 1,023 patients were identified to have at least one of the defined risk factors for chronic liver disease and eligible to be invited to attend the community risk stratification pathway (Table 1). Of these, 576 patients attended the pathway, of which 369 had obesity, 171 were diagnosed with type 2 diabetes, and 165 had been identified to have hazardous alcohol use."
		(b) Give reasons for non-participation at each stage	No	Not reported
		(c) Consider use of a flow diagram	No	No flow diagram provided
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	Baseline characteristics of the included (n=576) and all adult patients (n=4150) presented in Table 1.
		(b) Indicate number of participants with missing data for each variable of interest	No	Not reported
Outcome data	15*	Report numbers of outcome events or summary measures	Yes	66 patients (12.4%) had elevated TE reading consistent with clinically significant liver disease. Characteristics of those with and without elevated TE are in Table 3 & 4.
Main results	16	(*a*) Give unadjusted estimates and, if	Yes	Table 5, and odds ratios with 95% CI reported

	Item No	Recommendation	Judgement	Support for judgement
		applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		incorporating BMI, age, gender, type 2 diabetes, hazardous alcohol use, hypertension, hyperlipidemia, ischaemic heart disease, previous smoker.
		(*b*) Report category boundaries when continuous variables were categorised	Yes (in methods)	Hazardous alcohol use and obesity defined in methods.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	Proportion of patients with reliable and unreliable readings using the M+ and XL+ probes (Table 2). Number of patients with elevated TE by BMI category (Figure 1 & 2).
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	"In this study, obesity has been highlighted as a significant independent risk factor for detecting an elevated TE reading, whichis consistent with significant liver disease." "Furthermore, 31% of all the patients with an elevated TE reading (≥8.0 kPa) had obesity as their only risk factor".
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Authors acknowledge stratification pathway based on risk factors potentially biases the outcome; risk of liver disease in general population unknown. Response rate 56.3% comparable to other community based studies but may be subject to responder bias. All patients were identified from electronic records, therefore if a patient had not been asked about their alcohol use or AUDIT questionnaire completed, they would

	Item No	Recommendation	Judgement	Support for judgement
				not have been invited to participate.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	Authors acknowledge that TE is a surrogate marker for liver disease, and false positive may still occur because of steatohepatitis, cholestasis, and congestive cardiac failure, particularly in those patients who continue to drink alcohol. Authors confirm that this may lead to overestimation of liver disease.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	Authors recognise that "The only true way to determine whether these patients have been stratified correctly is to follow-up this cohort for long-term clinical outcomes." Relevance to clinical practice section.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	"Financial support: Funding for the study was provided by i) the Nottingham Digestive Diseases Centre and National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre part of the Nottingham University Hospitals NHS Trust and University of Nottingham and ii) The East Midlands Academic Health Sciences Network (EMAHSN). The study sponsor is the University of Nottingham, who are data custodians but had no role in the design, analysis, or interpretations of the data. All authors declare that they are free from other sources of external funding related to this study.

	Item No	Recommendation	Judgement	Support for judgement
				Potential competing interests: None to report. Disclosure: This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health."

*Give information separately for exposed and unexposed groups.

Harris *et al.* (2018); n=477 patients

First reviewer: KK; Second review: RO

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	Title: The XL probe: A luxury or a necessity? Risk stratification in an obese community cohort using transient elastography
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Objective (analyse the performance of two probes M/XL), methods (including setting), results and conclusions in abstract.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	CLD has increased. Raised BMI is associated with failed or unreliable TE measurement using standard M+ probe (successful readings in only 75% of obese patients of 30kg/m^2 or higher).
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"The aim of this study was to analyse the performance of the M and XL TE probes among those with a BMI≥28 kg/m^2 within a risk stratification pathway based in the community."
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	Prospective study. The study has been registered on the ClinicalTrials.gov website (NCT02037867).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	Single primary care practice, Leicester (January 2015 to March 2016). [Same time period as Harris *et al.* 2019]. Clinical, anthropometric and biochemical data was obtained from the electronic primary care records (SystmOne system), using READ codes.

	Item No	Recommendation	Judgement	Support for judgement
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes	Adults (at least 18 years) with one or more risk factors (hazardous alcohol use, type 2 diabetes, BMI at least 28 kg/m^2 recorded in past 5 years). "A lower BMI cut-off for obesity was agreed a priori for all patients within the study, due to the increased prevalence of patients with Asian ethnicity in this population."Patients with any of the following were not invited: contraindication to TE (pregnancy, implantable cardiac device), known diagnosis of CLD, known malignancy or other terminal illness, patients unable to consent to investigation or housebound and unable to attend.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	BMI (cut off for probe selection), age, gender, ethnicity, ischaemic heart disease, hypertension, hyperlipidaemia reported in baseline characteristics. Device failure, that is, inability to obtain 10 valid measurements. Unreliable acquisition if result at least 7.1 kPa and IQR/median ratio greater than0.3. Clinically significant liver disease diagnosed if result at least 8.0 kPa.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	Three experienced operators performed all TE measurements using portable FibroScan FS402 device. A TE reading was attempted with both probes for all patients.
Bias	9	Describe any efforts to address potential sources of bias	Yes	Univariate and multivariate analysis. Agreement between

	Item No	Recommendation	Judgement	Support for judgement
				probes analysed via Bland Altman analysis.
Study size	10	Explain how the study size was arrived at	No	Assumed to be total patient throughput of GP practice.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	"Baseline characteristics (Table 1) of the study cohort are presented as numbers (percentage) if categorical data or M (IQR) for non-normally distributed continuous data."
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	"comparison of then performance of both probes was made using the chi-squared test and the Wilcoxon signed rank test for categorical and non-normally distributed continuous data respectively." "Correlation between the liver stiffness measurements obtained by both probes was calculated and a linear regression analysis was completed to further characterise this relationship. Multivariable regression analysis was carried out to estimate the effect of potential confounding variables. Agreement between the probes was further analysed using a Bland-Altman plot. To identify variables independently associated with re-stratification, univariate and multivariate logistic regression models including the covariates age, gender, BMI, hypertension, hypercholesterolaemia, the reliability of the M+ probe reading, type 2 diabetes and hazardous alcohol use as risk factors were conducted."
		(*b*) Describe any methods used to examine	Yes	Multivariate analysis described above.

	Item No	Recommendation	Judgement	Support for judgement
		subgroups and interactions		
		(*c*) Explain how missing data were addressed	No	Not reported
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	"The primary care practice had a total adult population of 4150 with 1167 patients identified to have at least one risk factor and eligible to be invited to attend the risk stratification pathway. Of these, 720 patients attended of which 477 had a BMI≥28.0 kg/m2 and had TE readings attempted with both probes (patient characteristics outlined in Table 1)."
		(b) Give reasons for non-participation at each stage	Yes	As above
		(c) Consider use of a flow diagram	No	No flow diagram provided
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	Baseline characteristics of patients with TE measurements attempted with both probes given Table 1.
		(b) Indicate number of participants with missing data for each variable of interest	No	Not reported
Outcome data	15*	Report numbers of outcome events or summary measures	Yes	"21% of the patients had no valid measurements with the M+ probe." Reliability of probes presented in Table 3. "The TE readings between the probes were highly correlated (R^2=0.78, p value <0.001) (Figure 1)." Bland- Altman plot also presented (Figure 2).
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-	N/A	

	Item No	Recommendation	Judgement	Support for judgement
		adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		
		(*b*) Report category boundaries when continuous variables were categorised	Yes	Comparison of performance (Table 2).
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	Linear regression analysis (unclear how relevant given 95% limits of agreement are between -4.14 and 5.79 kPa).
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	"…use of TE with only the M+ probe as a risk stratification tool in an obese cohort could potentially lead to a large number of patients with an invalid or unreliable TE reading." "Linear regression analysis suggests there is a good correlation between the probes…[and] XL+ probe readings are lower than the M+ probe". "[The] difference is larger the greater the mean reading."
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Percentage of reliable readings lower than reported studies, however this study exclusively in obese patients. "This highlights the importance of having access to the XL+ probe in order to maximise the numbers of patientswho could be risk stratified." Unable to comment on diagnostic performance against histological findings (liver biopsy).

	Item No	Recommendation	Judgement	Support for judgement
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	Relevance to clinical practice section. "Our results demonstrate that 25% of patients with a BMI>30 kg/m^2 had an unreliable reading with the M+ probe. This therefore could be a practical threshold in which the XL+ probe should be considered ahead of the M+ probe. Alternatively, the M+ probe may soon become redundant if the XL+ probe is able to provide more reliable readings in a general population who are increasingly overweight and at risk of CLD."
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	"Thus, the XL probe is now not an optional extra but a necessity in a population setting where obesity is becoming routine."
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	"Echosens provided a loan of the XL probe at the start of the study. No financial assistance was provided and Echosens had no role in the study design, the collection or interpretation of the data. Funding for the study was provided by (a) the Nottingham Digestive Diseases Centre and National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre part of the Nottingham University Hospitals NHS Trust and University of Nottingham and (b) the East Midlands Academic Health Sciences Network (EMAHSN). The study sponsor is the University of Nottingham which is the data custodian but

	Item No	Recommendation	Judgement	Support for judgement
				had no role in the design, analysis or interpretations of the data." "All authors declare that they are free from other sources of external funding related to this study."

*Give information separately for exposed and unexposed groups.

Surey *et al.* (2019); 461 patients

First reviewer: KK; Second review: RO

	Item No	Recommendation	Judgement	Support for judgement
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	Identified as "observational study" in abstract.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Objectives, methods, results and conclusions in abstract. Focus on Hepatitis C virus (HCV) infection. Setting described in methods
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	HCV infection is a major cause of chronic liver disease and death. Disproportionately affects the homeless, people who inject drugs and prison populations, who also have difficulty in terms of testing, treatment and ongoing care.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	"This observational study assessed the burden of disease in an underserved population and describes the role of peer support in linking these individuals to specialist treatment services."
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	"a peer-led community outreach service" Peer support workers , trained in use of FibroScan by outreach workers, able to take individuals to clinical appointments as well as monitor treatment adherence.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	63 sites in London including drug and alcohol services, homeless day centres and homeless hostels over 109 sessions [from Results]. "Sites were identified if they were deemed to have a high proportion of individuals

	Item No	Recommendation	Judgement	Support for judgement
				with risk factors for HCV such as injecting drug use, and included homeless hostels, day centres and drug treatment services." Screened between September 2016 and May 2018 [from Results]. "Information was gathered on risk factors and demographic information at screening as part of routine patient care. Follow-up information regarding linkage to care and treatment outcomes was gathered by the contacting patients and support services by a member of the clinical team. All patient data were entered into a patient management system database and an anonymised extract of the data was analysed"
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes	"Inclusion criteria were being over 16 years of age, a willingness and ability to provide signed informed consent and being from an underserved population in the community. This was defined as groups whose social circumstances make it difficult to access services and could include people who are homeless, people who misuse substances and people exposed to the prison system."
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Partly	"Those testing positive, reporting a previous positive result or with risk factors for liver disease were offered a liver assessment using a portable FibroScan, which uses transient elastography to assess

	Item No	Recommendation	Judgement	Support for judgement
				liver fibrosis." Model not reported, diagnostic criteria not reported (only F1, 2, 3, 4) in table 1.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	No	Not reported
Bias	9	Describe any efforts to address potential sources of bias	No	Not reported
Study size	10	Explain how the study size was arrived at	No	Assumed to be site throughput, but not reported.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	No	Not reported
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	No	Not reported
		(*b*) Describe any methods used to examine subgroups and interactions	No	Not reported
		(*c*) Explain how missing data were addressed	No	Not reported
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	No	Not reported
		(*e*) Describe any sensitivity analyses	No	Logistic regression did not include transient elastography.
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	No	Partly provided in Table 2, but not reported in context of FibroScan (unclear how many were eligible for FibroScan, how many attempted/failed, and how many reliable)
		(b) Give reasons for non-participation at each stage	No	Not reported

	Item No	Recommendation	Judgement	Support for judgement
		(c) Consider use of a flow diagram	No	No flow diagram provided
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Yes	Table 1 is clearly written to allow calculation of how many missing each variable.
Outcome data	15*	Report numbers of outcome events or summary measures	No	FibroScan results only in Table 1.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No	Not reported
		(*b*) Report category boundaries when continuous variables were categorised	No	Not reported
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	Focus on HCV and treatment pathway. Unclear how FibroScan results influenced treatment pathway.
Discussion				
Key results	18	Summarise key results with reference to study objectives	Partly	However no mention of transient elastography or FibroScan.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Authors acknowledge lack of comparator group. Potential for selection bias (a number of patients were not contactable following referral and it is possible that they were more likely to have a negative outcome).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity	Partly	Many models of peer-support groups to "buddy" type interventions.

	Item No	Recommendation	Judgement	Support for judgement
		of analyses, results from similar studies, and other relevant evidence		"Qualitative studies have highlighted the importance of trust between peer and service user born out of a shared experience."
Generalisability	21	Discuss the generalisability (external validity) of the study results	Partly	Small number of motivated highly trained peers, therefore roll out of the model may not achieve same outcomes, "The majority of patients had been tested previously, suggesting that there is still a large pool of people who are disengaged from treatment services."
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	"Funding: This work is co-funded by the European Commission through its EU Third Health Programme (Grant Agreement Number 709844), University College London and University College London Hospitals NHS Trust. Transparency declarations: John Gibbons and Ala Miah work for Groundswell, which has received financial support from the pharmaceutical company Gilead. The remaining authors have none to declare. This article forms part of a Supplement sponsored by the HepCare Europe Project."

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix B3: Observational studies (STROBE: cohort)

Reinson *et al.* (2021); n=59 rescanned at 54 months follow-up.

First reviewer: KK; Second review: RO

	Item No	Recommendation	Judgement	Support for justification
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	From title: "follow-up study over 54 months". Cohort study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	4.5 year follow up after first "liver service" attendance that included TE in 5 GP practices in Southampton. Progression reported, and predictors explored.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	"How this fits in" section, liver disease annual cost and third biggest cause of premature mortality stated.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	3 aims: to determine whether alcohol and weight advice was effective after 4.5 years, liver rescan uptake and liver disease progression after 4.5 years.
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	Follow-up of LOCATE study (cites El-Gohary *et al*. 2018)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	"Rescans took place at two primary care sites in Southampton". Eligible patients were telephoned between August 2019 and May 2020. Alcohol AUDIT score and weight recorded, and eligible patients were rescanned and compared to baseline.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes	LOCATE study, eligible patients were alive at time point, agreed to be contacted for follow-up and had a baseline TE reading of at least 6kPa and less than 12kPa. Inclusion and exclusion criteria stated (additional

	Item No	Recommendation	Judgement	Support for justification
				information in Box S4 and S5 in Suppl Mat).
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	FibroScan readings, BMI, alcohol AUDIT scores. Binary logistic regression analysis used to test relationship between baseline independent variables and liver fibrosis stage at follow-up. Thresholds defined using TE kPa (e.g. >10kPa referred to secondary care hepatology clinic).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	TE: from FibroScan Mini+ 430 402 models. Patients reported weight and answered AUDIT alcohol questions.
Bias	9	Describe any efforts to address potential sources of bias	No	Not reported
Study size	10	Explain how the study size was arrived at	Yes	Follow-up of LOCATE study, including all eligible patients who consented.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	"A 15% coefficient of variation was applied to the rescan readings to reliably identify any changes to fibrosis stage between baseline and follow-up. Standard descriptive statistics were used to summarise variables: mean (SD) for continuous variables or median (IQR) for skewed variables, and numbers and percentages for categorical variables."
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	Paired sample t-test, chi-square test, two-tailed independent sample t-test, binary logistic regression analysis reported.

	Item No	Recommendation	Judgement	Support for justification
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	Relationship between baseline variables and liver fibrosis stage at follow-up.
		(*c*) Explain how missing data were addressed	No	Not reported
		(*d*) If applicable, explain how loss to follow-up was addressed	No	Not reported
		(*e*) Describe any sensitivity analyses	Yes	Different thresholds used for liver fibrosis stage (Table S3).
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	50.8% (n=59) patients were eligible for rescan, accepted the invitation and underwent a liver rescan. Fig 1, Suppl Table S1 and S2. Characteristics of those who were rescanned and those eligible are in Suppl Table S6.
		(b) Give reasons for non-participation at each stage	Yes	Fig 1
		(c) Consider use of a flow diagram	Yes	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	Table 2. Demographics of those taking part in weight and alcohol AUDIT follow up (Table S4, Table S5). Demographics of those with no change/decrease in fibrosis stage (Table S7).
		(b) Indicate number of participants with missing data for each variable of interest	Yes	Footnote in Table 2 (assume the remaining patients had complete data).
		(c) Summarise follow-up time (eg, average and total amount)	Yes	Mean (SD) time interval between baseline and follow-up was 53.6 (3.4) months.
Outcome data	15*	Report numbers of outcome events or summary measures over time	Yes	Reported proportions with change in liver fibrosis stage (no change, decreased, progressed)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	Yes	Table 1 and Suppl Table 7.

	Item No	Recommendation	Judgement	Support for justification
		confounders were adjusted for and why they were included		
		(*b*) Report category boundaries when continuous variables were categorised	Yes	Suppl Table S3 (however total adds to 58 not 59), Table S8, Table S9.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	Two separate binary logistic regression analyses to investigate relationship with regression or progression of liver fibrosis stage. Odds ratios reported in Suppl Table S10.
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	Advice had little impact on weight or alcohol consumption at 54months, 50.9% attended invitation of rescan at follow-up and none of the baseline factors were independently associated with progression.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Summary of main findings: no comparator group to determine significance of weight change (average of 1.2 kg). Strengths and limitations section: loss to follow-up, may have been a result of follow-up data collected during COVID-19 pandemic and included intermittent periods of restriction on movement in the UK, weight was self-reported (not verified).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	Comparison with existing literature includes a list of recommendations to improve adherence to clinical advice. Recommendations to GPs to ensure uptake by

	Item No	Recommendation	Judgement	Support for justification
				patients of low social economic status.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	Implications for research and practice section.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	Competing interests: The authors have declared no competing interests. Acknowledgements: This research was funded by the British Liver Trust (same as original LOCATE study) and Solent NHS Trust.

*Give information separately for exposed and unexposed groups.

Matthews *et al.* (2019); n=79

First reviewer: KK; Second review: RO

	Item No	Recommendation	Judgement	Support for justification
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	"Prospective observational study" stated in abstract, cohort assumed from monitored compliance over a 6-month period. "Pilot" not mentioned in abstract, but referred to in aims and objectives section.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Setting: nurse-led outreach community alcohol support clinic, with referrals to specialist care monitored. Background, methods and results well reported.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	Third most common reason for premature death in UK, mortality rates increased 500%. Cirrhosis is often asymptomatic and associated with long-term complications.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	The main aim of the pilot study was to determine acceptability of FibroScan in a community alcohol support service (patients present themselves if concerned about liver health due to alcohol consumption – may be selection bias).
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	"Prospective quantitative observational study"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	One community alcohol support setting in Edinburgh, over 12 month period (November 2014 until end October 2015). Screening with FibroScan offered during first 6 months

	Item No	Recommendation	Judgement	Support for justification
				until April 2015, and onward referrals recorded thereafter.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up		Convenience sample (due to measurement of acceptability) in one community alcohol support setting (Edinburgh). Number of individuals attending a research clinic over a 24-week period after reading a participant information pack. Inclusion criteria: aged over 16 years, ability to provide consent, attending triage facility for assessment of their support needs, or who were currently undergoing alcohol support in the centre. Exclusion: possibility of or known pregnancy, pacemaker, ascites, open wound close to right eighth to tenth intercostal margins, known cirrhosis or no alcohol history. Study was advertised by rolling TV screen in reception area, posters in reception and consultation rooms – participants could then volunteer (source of bias).
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	Focused medical and lifestyle history taken by hepatology nurse (data collection tool provided as Appendix 1 including: height, weight [BMI calculated], alcohol, medical, smoking, family history, current medication, possible viral hepatitis risk). Lower cut-off measurement of 7.1kPa for referral to nurse-led

	Item No	Recommendation	Judgement	Support for justification
				clinic. Ultrasound and clinical evaluation by consultant hepatologist when FibroScan at least 8kPa.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	Portable FibroScan (model not reported). Data collection form provided. How and where FibroScan was measured described.
Bias	9	Describe any efforts to address potential sources of bias	No	Not reported
Study size	10	Explain how the study size was arrived at	Yes	Convenience sample. "As this study evaluated the acceptability of the cirrhosis screening intervention in this setting, no specific sample size was determined in advance."
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	Follow-up based on FibroScan results reported.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	No	Not reported
		(*b*) Describe any methods used to examine subgroups and interactions	No	Not reported
		(*c*) Explain how missing data were addressed	No	Not reported
		(*d*) If applicable, explain how loss to follow-up was addressed	No	Not reported
		(*e*) Describe any sensitivity analyses	N/A	None conducted
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	118 patient information packs requested (reported in methods only), 79 service users consented to take part.

	Item No	Recommendation	Judgement	Support for justification
		(b) Give reasons for non-participation at each stage	No	Not reported (assume all 79 met inclusion criteria)
		(c) Consider use of a flow diagram	No	No flow diagram provided
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	Table 1 (total, male, female)
		(b) Indicate number of participants with missing data for each variable of interest	No	Not reported, except for missing (that is, invalid) FibroScan reading in three participants.
		(c) Summarise follow-up time (eg, average and total amount)	No	Only reported that nine of ten patients expected to attend a six-monthly follow-up did so. However the remaining patients not followed.
Outcome data	15*	Report numbers of outcome events or summary measures over time	Yes	Diagnostic outcomes (cirrhosis, fibrosis) included in Table 2.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No	Not reported
		(*b*) Report category boundaries when continuous variables were categorised	Yes	Category boundaries for FibroScan included in Table 2, alcohol intake categorised in Table 1.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	Patient engagement: "Of the 20 participants referred to the nurse-led service clinic within the alcohol service, 19 attended. Of the 12 patients expected to attend the RIE for medical assessment, 11 did so, and of 10 patients expected to attend for six-monthly follow-up, nine did so. All 12

	Item No	Recommendation	Judgement	Support for justification
				patients referred for abdominal ultrasound attended."
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	Summary of engagement (first paragraph of discussion).
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Authors acknowledge recruitment was based on a "drop-in" system, unclear if volunteered participants were representative (demographics) of the community clinic population. Fixed term study, longer study needed to determine whether engagement and lifestyle changes were sustained.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	Authors acknowledge further work required to optimise the intervention and to determine long-term impact.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	Relevance to clinical practice section.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	"NHS Lothian Innovation Board provided £6200 funding for rental of the FibroScan device for the six-month duration of data collection from November 2014 to April 2015. NHS Lothian Research Futures for providing funding to cover fees for doctoral level study and educational needs pertinent to developing the study for dissemination. Conflict of interest: none."

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in

conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Appendix B4: Qualitative studies (CEBM)

Knight *et al.* (2020); n=20

First reviewer: KK; Second review: RO

#	Question	Judgement (Yes/No/Unclear)	Justification
1	Was a qualitative approach appropriate?	Yes	Patient acceptability and experience of new screening service in primary care setting.
2	Was the sampling strategy appropriate for the approach?	Yes	Sampled from a large cross-sectional study (Nottingham Community Liver Study). Patients had attended a TE assessment 6 months to 2 years before data collection. However the authors state in their limitations that the characteristics of individuals who declined to participate were not stored following their decline (risk of selection bias). Non-English speaking participants were excluded (liver disease is known to vary widely among ethnic groups). Authors note narrow age of interviewees (40-71 years), however notes that this reflects the ages where people are most at risk of chronic liver disease.
3	What were the data collection methods?	Yes	"Interview questions were predominantly open-ended with probes used where necessary to expand on participant responses"(Appendix 1: Interview Guide). Guide was piloted on 3 participants for testing and refinement. Face-to-face interviews conducted over 6 month period (dates not defined). "Interviews took place either in the participant's home (n=14) or in an interview room at a tertiary care centre (n=6) [participant choice]". "Interviews continued until data saturation was reached" (undefined). "Interviews were digitally audio-recorded and transcribed verbatim by a specialist

			transcription company." Study team attempted to minimise response bias by notifying all participants that their interview transcripts would be anonymised. The authors acknowledge that "the interviewer was involved in the larger community study and had met the participants with elevated liver stiffness", which may have impacted results.
4	How were data analysed and how were these checked?	Yes	Analysed thematically using an inductive approach. Preliminary scan and then coded, sorted and grouped into categories or themes. "A constant comparative method was used to compare individual items with the rest of the data." Independent coding of 5 interviews by a different reviewer. Themes refined, reorganised and collapsed as required. Data management tool reported.
5	Is the researcher's position described?	Yes	MB: independent qualitative researcher DH: interviewer
6	Do the results make sense?	Yes	Descriptive narrative analysis with quotes taken from survey responses. Responses seem logical.
7	Are the conclusions drawn justified by the results?	Yes	Broad summary in line with results.
8	Are the finding transferable to other clinical settings?	No	Specific to primary care setting (however authors state that purposefully sampling from inner city and suburban locations with different CLD risk factors and CLD diagnoses may allow transferability to similar primary care settings within the UK). Participants were asked to comment on their experience of a scan 6 months-2 years prior, and may have engaged with other liver disease services (potential for recall bias).

Appendix C: Ongoing studies

Appendix C1: Completed studies with no publication

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
Southampton Pilot Study – *identified by the Company* [No registration found] UK	Status: Unknown Expected completion: 2020	Actual enrolment: n=116 Patients are 18 years and over, registered with a Southampton City CCG GP and with a ELF test result not less than 9 or alcohol consumption more than 30 units per week.	FibroScan examination attendance	Referrals to Hepatology versus discharged back to GP; Hospital first outpatient activity.
Liver disease early detection study – *identified by the EAC* [ISRCTN40804377] UK: 8 GP surgeries	Status: Completed Trial end date: 18 July 2015 Last update: 3 May 2017	Target enrolment: n=90 Inclusion criteria: Participants from the previous study ALDDES who were found to be at a possible or probable risk of liver fibrosis. Exclusion criteria: Known pre-existing liver disease.	Positive predictive value of Southampton Traffic Light Test; [On assessment with liver elastography]	None listed.

Appendix C2: Ongoing studies

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
Impact of knowledge of liver fibrosis on drinking behaviour – *identified by EAC* [ISRCTN16922410] UK	Status: Recruiting Estimated completion: 30 November 2022 Last update: 15 June 2021	Target enrolment: n=120 Inclusion criteria: Work package 1 (WP1): A person aged 18 years and over attending with a primary problem of alcohol misuse as defined by initial clinical assessment and had a fibroscan in past; Willing to participate in a focus group. Work package 2 (WP2): A person aged 18 years and over attending with a primary problem of alcohol misuse as defined by initial clinical assessment; A person who previously had a fibroscan; A person with lived experience of alcohol problems, willing to consent to the recording and public use of video recording (identified via KLIFAD PPI group, existing NRN networks or research	Recruitment rate recorded as the number of eligible participants who consent to participate in the study [12 months]; Retention rate: number of participants who consent to participate that remain in the study until the end of follow up [6 months]; Acceptability of the intervention measured using qualitative interview [6 months]; Feasibility of outcome measures measured by analysing the feasibility of outcomes outlined as primary and secondary [baseline, 3 months and 6 months].	Weekly alcohol intake measured using self-reported alcohol intake [baseline, 3 months and 6 months]; Alcohol misuse measured using AUDIT score [baseline, 3 months and 6 months]; Severity of alcohol misuse measured using SADQ score [baseline, 3 months and 6 months].

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
		networks at Nottingham University Hospital) Participants from WP1 will also be invited to participate in WP2. Randomised feasibility trial (WP3): A person aged 18 years and over attending with a primary problem of alcohol misuse as defined by initial clinical assessment. Exclusion criteria: Work package 1 (WP1): Other primary substance misuses even where alcohol is a factor; Lacks the capacity to give confirmed consent. Work package 2 (WP2): Lacks the capacity to give confirmed consent. Randomised feasibility trial (WP3): Other primary substance misuses even where alcohol is a factor; Referrals from driving		

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
		offences and student referrals as these individuals are essentially not self-presenting, may have different motivation and have lower overall levels of alcohol use and so are substantially lower risk of having liver disease; Out of area clients at Edwin house in whom we cannot obtain follow up data due to lack of follow up availability; Participants unable to comply with study procedures; Lacks the capacity to give confirmed consent.		

Appendix D: Critical appraisal of economic evidence

Appendix D1: Published economic evidence

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

CHEERS Checklist: Tanajewski *et al.* (2017)
Items to include when reporting economic evaluations of health interventions

First assessment: RO, QA: RP/KK

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Y	Title includes "economic evaluation" and "Markov model". Objectives in abstract: "To assess the long-term cost-effectiveness of a risk stratification pathway, compared with standard care, for detecting non-alcoholic fatty liver disease (NAFLD) in primary care."
Abstract	2	Provide a structures summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses) and conclusions.	Y	Objectives, setting, participants, intervention, design, data sources (assumed inputs), outcome measure, results (including base case and uncertainty analyses) and conclusions, all reported in abstract. Perspective not explicitly reported, although setting reported as GP practices in England (NHS England perspective mentioned in Introduction); costs reported in GBP.
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Y	Authors report that prevalence of NAFLD is rising, and will continue to do so due to increasing prevalence of obesity and type 2 diabetes, and will lead to increased prevalence of cirrhosis. Existing screening tests being poorly sensitive

				means they cannot rule out liver disease, and poor specificity potentially leads to more invasive investigations and specialist referral. Prospective study has shown increased detection of liver disease in primary care, using TE. Aim of study is to evaluate the cost-effectiveness of a risk stratification pathway, compared with standard care, from an NHS England perspective.
Methods Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Y	Base case population reported as being from two primary care practices in Nottingham, with 3.7% type 2 diabetes prevalence, and 14.9% obesity prevalence. Of the included patients (n=293), mean (SD) age was 68.4 (12.6) years. Patients with a history of excessive alcohol use were excluded. "The initial distribution of patients between the three liver disease stages was assumed to reflect the distribution of patients stratified by RSP in the feasibility study: 69% no/mild liver disease, 27% significant liver disease and 4% compensated cirrhosis."
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Y	"The RSP [*risk stratification pathway*] is a community-based diagnostic algorithm..."
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Y	"…we investigated the cost-effectiveness of this risk stratification pathway (RSP), compared with SC, from an NHS England perspective." Not explicitly related to the costs being evaluated, but costs reported in GBP and authors report using NHS reference costs and PSSRU.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Y	RSP and standard care fully described in methods section. Rationale for choosing them not reported in methods, but introduction refers to the prior feasibility study on which this economic evaluation is based.

Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Y	The authors report a lifetime horizon (to 100 years of age), justified in conclusion/future perspective section as patient benefits related to chronic condition are long-term.
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Y	The "UK Treasury recommended 3.5% discount rate for costs and outcomes were used."
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Y	Health states defined: illustrated in Figure 1: mild disease (true/false), significant liver disease (true/false), compensated cirrhosis (true/false), decompensated cirrhosis, hepatocellular carcinoma, liver transplant and death. A stochastic probabilistic model was developed.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Partly	"Individual-patient data from the feasibility study were used to generate input parameters related to RSP and SC target population characteristics and diagnostic effectiveness." Feasibility study was prospective and cross-sectional, including 2 primary care practices in Nottingham (10,479 adult patients). No justification given for this being sufficient source of effectiveness data (however is large, NHS perspective).
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A	N/A – single study-based estimate
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Y	"An expert panel of UK hepatologists was convened to generate indicative estimates where no data were available (see Table 1 for transition probabilities and sources; elicitation methods provided in online supplementary appendix 2, figure 2.1 and table 2.1)." No studies reporting utilities for NAFLD health states were found; expert opinion QoL data were approximated using QoL data from type 2 diabetes.
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for	N/A	

		valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.		
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Partly	"Due to a paucity of data in some areas, an expert advisory panel was convened to generate indicative estimates of transition probabilities and resource use." "Resource use for each health state was estimated based on published literature, UK local and national guidelines and international clinical practice guidelines from EASL and the American Association for the Study of Liver Disease. These estimates were checked for validity with the expert panel." See Table 2. "Where a cost could not be identified, a literature search was conducted or local finance departments were contacted." No opportunity costs included.
Currency, price, date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Y	References NHS Reference costs 2013/14 and PSSRU 2014. "Where a cost could not be identified, a literature search was conducted or local finance departments were contacted. All costs were inflated to the 2013/2014 financial year." All costs reported in GBP, so no currency conversion required.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Y	Decision-analytic model described and shown in Figure 1. Illustrates that the decision tree allows comparison between the two diagnostic pathways, while the Markov model (identical for both arms) accounts for subsequent pathway and outcomes during lifetime modelling.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Y	All assumptions described (additional information in supplementary material). Death possible from every state (Figure 1).
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Y	"The data inputs used to populate the model provide a measure of uncertainty around the estimates. An annual cycle length with half-cycle correction…[was] used." Estimates were checked for validity with the expert panel. Data were specified as distributions to fully incorporate uncertainty around parameter values for probabilistic analysis (5000 iterations).

Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Partly	Values, references, and probability distributions (where appropriate) reported in tables 1 and 2. However distribution parameters not explicitly reported.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Partly	Mean lifetime costs reported for each group, and difference between groups, QALY and ICER, but not broken down into main categories or outcomes (totals only).
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Y	Results for one-way and multi-way deterministic sensitivity analysis, and probabilistic sensitivity analysis reported (Table 3, Tornado diagram Figure 3). However, result of PSA (cost saving £512) not consistent with point estimate (cost saving £225).
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N	No subgroup analysis reported, and may have been appropriate given the different risk factors for NAFLD in the population included.
Discussion				
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Y	Concludes that the Risk Stratification Pathway is likely to be cost-effective in the UK, even in the presence of significant uncertainty around estimates. However the EAC notes that ICER (£/QALY) was -1010 [95%CI -40,583 to +50,023]. Limitations reported include complexity of the model limiting inclusion of wider health benefits, extensive lack of appropriate data to underpin the model, unknown sensitivity and specificity of TE in primary care (due to practical and

				ethical issues around performing liver biopsy in this setting). Generalisability acknowledged to be limited by discrepancies between obesity and type 2 diabetes prevalence estimates in study and general population, and by not including patients with all metabolic syndrome risk factors (included type 2 diabetes only). Limited reporting of current knowledge, although clinical implications and future perspectives considered.
Other				
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Y	"This work was funded by the East Midlands Academic Health Science Network (EMAHSN) and the University of Nottingham." Not explicitly stated that funders had no involvement in identification, design, conduct or reporting of the study, but may be assumed: "All authors take full responsibility for the study design, model assumptions, data analysis and interpretation, and preparation of the manuscript."
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Y	"Competing interests: None declared." "Provenance and peer review: Not commissioned; externally peer reviewed."

CHEERS Checklist: Crossan *et al.* (2019)
Items to include when reporting economic evaluations of health interventions

First assessment: RO, QA: RP/KK

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Yes	"Referral pathways for patients with NAFLD based on noninvasive fibrosis tests: Diagnostic accuracy and cost analysis". From abstract: 3 referral strategies were modelled. Non-invasive fibrosis tests included: FIB-4 followed by FibroScan, ELF, or FibroTest.
Abstract	2	Provide a structures summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses) and conclusions.	Partly	Objectives (investigation of diagnostic accuracy and costs), setting (primary care), and conclusions reported in abstract. Results stat cost savings but do not report magnitude or 95% confidence interval. Perspective and methods (study design and inputs) not explicitly defined.
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Y	"Given the low prevalence of AF in unselected patients with NAFLD, [non-invasive fibrosis] tests or their combination have high negative predictive value and can be used to guide referrals for dedicated hepatology input and provide an efficient solution for improving outcomes. We therefore modelled a pathway using non-invasive fibrosis tests in PC to triage patients for SCRs based on diagnostic accuracy and decision curve analysis. We subsequently carried out a cost analysis of different scenarios of this pathway."
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Y	Modelling study only, so no characteristics to report beyond "We considered a hypothetical cohort of 1000 unselected patients with NAFLD who are tested for the presence of AF." "We set the prevalence of AF (≥F3) in the PC

				population at 5%, similar to what is expected in unselected cohorts with NAFLD."
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Y	"We present modelling and cost data of a two-step pathway to appropriately triage patients in primary care."
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Partly	Perspective not explicitly described, but assumed to be UK NHS based on: "We assumed that the cardiovascular management would be done by the general practitioner (GP) (as is customary in the UK)". Costs expressed in GBP
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Y	All scenarios described, and also shown as a schematic in Figure 1. Single and two-tiered approaches described in Table 2 and Figure 2.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Y	"The time frame adopted in the analysis was 5 years…". "We assumed that all patients who test negative at baseline (TN and FN) would be re-tested at 5 years in order to diagnose those with disease progression and those who tested FN in the first instance".
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Y	"…discount rate of 3.5% was applied" and references NICE methods guide
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Y	"The outcomes considered were true/false positives and true/false negatives with associated mortality, complications, treatment and follow-up depending on the care setting." This includes referrals to secondary care and biopsy.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	N/A	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Y	"We sourced the summary sensitivity and specificity of these NITs from a systematic review and meta-analysis of the diagnostic accuracy of NITs compared to liver biopsy in adult patients with NAFLD [ref 9]. This was part of a larger project funded by the UK NIHR Health Technology Assessment Program that determined the cost-effectiveness of NITs in patients with HBV, HCV, ALD and NAFLD [ref 9-11]."

Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A	No preferences for outcomes elicited.
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Y	Estimation of consultations, medical treatment and interventions well reported in paper. Unit costs reported in supplementary material (suppl Table 1,) sourced from DoH, NHS reference costs, PSSRU, personal communication with Royal Free labs, NICE guidance, CELT study.
Currency, price, date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	N	Dates of resource not consistently reported in Suppl Table 1), adjustments and inflation not described. All costs reported in GBP, and the majority identifiable as UK sources, so unlikely to have required currency conversion.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Y	Decision curve analysis described and justified ("Decision analysis and net benefit" section), schematic of testing pathways shown in figures 1 and 2.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Y	Assumptions described in section 2.3.1 Assumptions regarding resource use.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Y	"Net benefit was calculated and expressed across a range of threshold probabilities as decision curves and net reduction in intervention curves, according to the method described by Vickers and Elkin [ref 19]." "We opted to use a rudimentary cost analysis rather than Markov modelling as there is too much uncertainty in the assumptions for the latter, because of the lack of relevant long-term data about the natural history and treatment." Sensitivity analysis included prevalence of advance fibrosis and tiered approach.

Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Y	Diagnostic accuracy reported in Table 1, results in Table 2.No distributions described as the reported sensitivity analysis focused on three well-specified scenarios (no PSA conducted).
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Partly	Mean total cost per person reported in table 3, and in supplementary material, for each scenario. Costs per test outcome reported in Suppl material, however subsequent costs of complications, biopsy secondary referral not explicitly reported.Differences between scenarios not explicitly reported (EAC assume this is due to none of the scenarios representing current standard care; all representing exploratory analysis).
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Y	Sensitivity analysis reported for three scenarios, using single and two-tiered approaches, varying advance fibrosis prevalence. Uncertainty regarding long-term outcomes not included due to lack of data.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Y	Results of sensitivity analysis reported for three scenarios, accounting for subgroup with increased prevalence of advanced fibrosis, use of NAFLD fibrosis score instead of FIB-4 as first line test, and use of dual FibroScan cutoffs. Net benefit (including reduction in biopsies) described in Table 4 and Suppl material (Table 5) at various threshold probabilities.
Discussion				
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Y	"Our findings support a two-tier approach, with FIB-4 as the initial triaging test, followed by ELF, Fibroscan or FibroTest in patients with an indeterminate FIB-4. This would result in a referral rate of approximately 10% and cost savings of at least 40% compared to the 'refer all' strategy." Authors

				acknowledge limitations regarding generalisability of the model; optimised for patients aged between 45 and 60 years. Authors state other economic evaluations have high risk of selection bias and likely overestimate risk of disease progression.
Other				
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	N	No funding source reported. Only funding declared relates to systematic review and meta-analysis (by NIHR HTA) from which sensitivity and specificity values for non-invasive fibrosis tests were obtained.
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Y	"WR and MP are inventors of the ELF test but receive no related royalties. WR and AS have received speakers' fees from Siemens Healthineers. The other authors declare no competing interests." Individual author contributions also listed.

CHEERS Checklist: Srivastava *et al.* (2019)
Items to include when reporting economic evaluations of health interventions

First assessment: RO, QA: RP/KK

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Y	"Cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for nonalcoholic fatty liver disease"
Abstract	2	Provide a structures summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses) and conclusions.	Y	Objectives (to assess clinical and cost differential of different non-invasive liver fibrosis test strategies), perspective (healthcare payer, costs reported in GBP), setting (primary care), methods (study design: probabilistic decisional model with simulation of 1000 NAFLD patients over 1 year, inputs: "derived from the published literature", outcomes: cost per case of advanced fibrosis detected), results (baseline and scenario analysis), and conclusions all reported.
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Y	"With rising prevalence of risk factors for liver disease including obesity and alcohol…[b]etter and earlier detection of CLD in primary care is key to improving health outcomes and associated costs" "The use of non-invasive liver fibrosis tests (NILT) [ref 14] may improve PCP staging of disease [ref 4, 15] and referral practice but there is a lack of health-economic evidence about the use of NILT in fatty liver disease to inform clinicians, commissioners and policy makers about the value of such strategies. In this study, we developed a probabilistic decision analytical model to investigate the clinical and cost impact of primary care risk stratification of patients with NAFLD."
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Y	Modelling study only, so no characteristics described except "…1000 patients with a confirmed diagnosis of NAFLD

				(Fig. 2). The average patient was 50 years old with elevated transaminases." No subgroups reported or analysed.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Y	"In this study, we developed a probabilistic decision analytical model to investigate the clinical and cost impact of primary care risk stratification of patients with NAFLD."
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Y	"We modelled the standard care in the UK National Health Service (NHS)." and reference to "healthcare payer perspective" in abstract.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Y	All five simulated scenarios described in methods, and depicted in flow diagrams in Figure 3. Rationale for choosing strategies being compared assumed to be: "The use of non-invasive liver fibrosis tests (NILT) may improve PCP staging of disease and referral practice but there is a lack of health-economic evidence about the use of NILT in fatty liver disease to inform clinicians, commissioners and policy makers about the value of such strategies."
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Y	"The time horizon for the base-case was 1 year to assess short-term benefits, likely to relate to resource utilisation. A 5- year timeframe was applied to assess the longer-term implications."
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Partly	"A 3.5% discount rate was applied." However, no reason given and no reference.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Y	Reported cost per case of advanced fibrosis detected, costs associated with early and late stage complications, and liver transplant.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	N/A	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Partly	"A comprehensive literature search informed model parameters." However no details provided, and no reference. Test performance given in Table 1, with sources

				(including expert opinion). Transitional probabilities reported in Table 2, with sources. "The data were critically assessed to ensure suitability for this study and were supplemented by expert opinion when required."
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N	"The data were critically assessed to ensure suitability for this study and were supplemented by expert opinion when required." No additional detail provided. Utility measured by proxy of detection of advanced fibrosis.
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Y	Resource use and costs well described and referenced (Table 3). Source includes Royal Free London NHS Foundation Trust finance department. Opportunity costs (related to people not attending appointments) not included.
Currency, price, date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Partly	Table 3 reports dates of costs as 2014 to 2015 (publication 2019 with no adjustment). All costs reported in GBP, so no currency conversion necessary.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Y	Model described as decision tree, with structure shown in Figure 2. Structure justified in Discussion as "our main economic focus was on the payer perspective rather than a population health perspective, where alternative costeffectiveness approaches using quality of life data and Markov simulations would be desirable. The lack of beta or triangular distributions and true probability sensitivity analysis limits the model. The model lacks cost/ QALY data

				and relies on descriptive measures including cost per case of advanced fibrosis detected."
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Y	No assumptions formally reported in methods, structural assumptions illustrated in Figure 2. Additional assumptions reported in discussion, one assumption reported in Table 2, and others mentioned in the context of sensitivity analysis.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Partly	One-way sensitivity analysis (patient uptake, specificity of advanced fibrosis detection). No formal PSA conducted.
Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Y	Inputs defined in Tables 1, 2, and 3. Ranges provided with results of sensitivity analysis. No probabilistic sensitivity analysis performed, so no distributions given.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Y	Table 5 describes budget impact analysis of FIB-4, ELF and FibroScan in primary care risk stratification pathways compared with standard care (total and by main category). Table 6 reports costs per fibrosis of at least F3 detected, and cost savings for each scenario when compared with standard care (including referrals avoided, and cases cirrhosis detected and missed). Table 7 reports costs for each scenario for early and late stage complications, and liver transplant, plus total costs for 1,000 NAFLD patients, and costs per advanced fibrosis detected.
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A	

	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Partly	Limited univariate sensitivity analysis reported.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Partly	No subgroups considered, however different scenarios explored (Table 4); same baseline characteristics of modelled 1000 NAFLD patients assumed across scenarios
Discussion Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Y	"Our cost consequence analyses indicate that the use of NILT [*non-invasive liver fibrosis* tests] to stratify patients with NAFLD in primary care is clinically effective and cost saving. Utilizing fibroscan alone was most effective in detecting patients with advanced fibrosis, whilst employing FIB-4 and ELF delivered the greatest cost saving." Limitations acknowledged include reliance on expert opinion in the absence of high quality published data, reliance on test performance data from use in secondary care, assumption that test performance is comparable when used first- and second-line. References to current knowledge, and limitations on generalisability reported in terms of diagnosing NASH, and influence of comorbidities on results of serum tests. Authors acknowledge "Additionally, there is no published randomised controlled trial exploring the performance of NILT in primary care." "The costing in the model is comprehensive, assuming full adherence to guidelines and protocols and thereby potentially overestimating the cost of care."
Other Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Y	"This work was supported by an unrestricted grant from Siemens Healthineers. The funder had no role in the design of the study, collection, analysis and interpretation of data or writing the manuscript."

Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Y	"AS, JP and WR have received speaker bureau from Siemens Healthineers; AS, SJ and WR have received support for research from Siemens Healthineers; WR is a NIHR Senior Investigator and is supported by the UCLH NIHR BRC. EP is supported by the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North Thames at Bart's Health NHS Trust. The views expressed are those of the author (s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. The other authors have no competing interests."

CHEERS Checklist: Serra-Burriel *et al.* (2019)
Items to include when reporting economic evaluations of health interventions

First assessment: RO, QA: RP/KK

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Y	"Transient elastography for screening of liver fibrosis: Cost-effectiveness analysis from six prospective cohorts in Europe and Asia". Abstract: "We compared the incremental cost-effectiveness of a screening strategy against standard of care alongside the numbers needed to screen to diagnose a patient with fibrosis stage ≥F2."
Abstract	2	Provide a structures summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses) and conclusions.	Partly	Objectives (TE as a screening method to detect liver fibrosis in primary care), perspective (Europe and Asia, costs reported in Euros), setting (primary care), method (design: cost-effectiveness analysis, results (range of ICER reported), conclusions (cost-effective and may be cost-saving). Inputs not explicitly reported.
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Y	Early detection of NAFLD and ALD, before advanced fibrosis develops, might be more beneficial and cost-effective as it allows for timely lifestyle interventions, patient guidance and disease monitoring. Study aims reported with mention to communities and healthcare systems.
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Y	"Patients from 7 previous independent prospective studies that have used TE (FibroScan) as a screening method for liver fibrosis detection were included in the study. The final cohort includes 6,295 patients from 6 different countries.." Differences between countries and cohorts described in Methods. Baseline characteristics of the six included cohorts reported in Table 1. No specific mention of subgroups but those with specific risk factors (obesity, diabetes, alcohol related risks) reported independently in Results.

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Y	Reported as "in a primary care setting."
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Y	"The perspective of the economic model was generated with provider-direct costs only". Mulitple countries included.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Partly	"This economic model compares 2 different pathways of detection and risk stratification for advanced chronic liver disease (significant fibrosis) in adults with suspicion of NAFLD or ALD in a primary care setting. One pathway uses TE and the other pathway uses aminotransferase activities (as standard of care) to detect patients with chronic liver disease." Assumption is that aminotransferase activity is the standard of care (large assumption).
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Y	Reported as "30-year time horizon", discussion reports long-term outcomes of patients with chronic liver disease.
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Partly	Reported as "3% discount rate on both health outcomes and costs", but no justification given, no reference provided.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Y	"The optimal cut-offs defined in our set of biopsied patients were used to infer the predicted fibrosis prevalence rates in each of the heterogeneous cohorts." Authors reported fibrosis stage, and subsequently number needed to screen to identify one case of fibrosis stage F2 or above in the general population, and those with obesity, diabetes or high risk alcohol consumption.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	N/A	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Partly	"Patients from 7 previous independent prospective studies that have used TE (FibroScan) as a screening method for liver fibrosis detection were included in the study." Methods for identifying and selecting included studies not described.

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
				Conditional inference tree using five-fold cross validation, used to establish diagnostic accuracy for F0 to F1, F2 to F3 and F4 fibrosis.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A	No mention of experts (can only assume expert advice not required)
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N	Resource usage not described in main text. "…several assumptions had to be made, mostly regarding care and cost structure…The only difference applied to the modelling setting was in the elastography testing cost structure, which is described in the Appendix; details of the assumptions, states and transition probabilities of the present study are also presented there." However, no appendix or supplementary material found by EAC.
Currency, price, date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Partly	"Costs are in 2017 Euros, purchasing power parity (PPP) was adjusted for all 6 countries." Exchange rates not given, no reference provided.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Partly	"The results of the 6 screening program cohorts were used in the parameter tuning of a previously published cost-effectiveness model": reference to Tanajewski *et al.* 2017. Structure of conditional inference tree shown in Figure 4, but economic model not shown.

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Partly	Authors acknowledge assumptions in line with Tanajewski *et al* (2017), and state assumptions are presented in the appendix, which could not be found.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Y	Analytical methods described in Statistical analysis and Economic modelling sections. Results reported separately for each country. PSA conducted to account for uncertainty.
Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N	"probabilistic sensitivity analysis was performed for [care and cost structure, rate of fibrosis progression, treatment effectiveness in different fibrosis stages] to account for the level of uncertainty associated with the estimates" but no further detail provided. No tabulated input values.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Partly	Only incremental cost-effectiveness ratios reported for Spain and Hong-Kong (ICER for other countries not reported). Differences between all countries not explicitly reported.
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Partly	Cost-effectiveness model survival estimates by fibrosis group and diagnostic arm reported in Figure 5. No additional sensitivity analysis reported.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline	Y	Results presented for each included cohort, and subgroups: obese, diabetic, alcohol related risk (Table 4). Baseline characteristics between 6 countries included in study reported in Table 1.

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
		characteristics or other observed variability in effects that are not reducible by more information.		
Discussion Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Y	Summarised that non-invasive screening for liver fibrosis is cost-effective. Acknowledges limitations that only 5.5% of included patients underwent liver biopsy, some assumptions were made in the economic modelling, unclear whether FibroScan is best used as a first-line or second-line test after serum biomarkers. "In our study, data from the subset of patients who had undergone liver biopsy was used to define the diagnostic cut-offs for significant liver fibrosis." Refers to earlier detection of fibrosis allowing timely referral, enrollment into surveillance programmes, and adequate treatment, with which the disease may regress.
Other Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Partly	"EIT Health project 2018, project number EIT 18258; BMBF Liver Systems Medicine, project number LiSyM 031L005; the Danish study was funded by Innovation Fund Denmark, the European Union's Horizon 2020 Research and Innovation Program (grant agreement number 668031). This study was funded by a grant awarded to PG (PI16/00043), integrated in the Plan Nacional I + D + I and co-funded by ISCIII-Subdirección General de Evaluación and European Regional Development Fund FEDER." "The LiverScreen Consortium is a group of institutions from Europe that have the objective of investigating population-based screening for chronic liver diseases. P. Ginès is a recipient of an ICREA Academia award." Role of funders not reported.
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical	Y	"MS, IG, LC, MT, DR, WS, NG, NF, RH, GW, SM, AK, PA, AA, PT, LC and FL have no conflicts of interests. IG has received lecture fees from Gilead and Novartis. P. Ginès reports grants and personal fees from Grifols, grants and

Section/item	#	Recommendation	Reported (Y/N)	Additional comments
		JournalEditors recommendations.		personal fees from Gilead, grants from Mallinckrodt, personal fees from Promethera, personal fees from Martin Pharmaceuticals, grants from Ferring Pharmaceuticals, grants and personal fees from Sequana. V. Wong has served as a consultant or advisory board member for AbbVie, Allergan, Echosens, Gilead Sciences, Janssen, Perspectum Diagnostics, Pfizer and Terns; he has also received lecture fees from Bristol-Myers Squibb, Echosens, Gilead Sciences and Merck."

Appendix D2: Critique of Company *de novo* model (Drummond checklist 1996)

First assessment: RO, QA: RP/KK

Item	Judgement				EAC comment
	Yes	No	Not clear	Not appropriate	
Study design					
1*. The research question is stated.	X	¨	¨		"The intervention being assessed is FibroScan done outside secondary or specialist care (for example, GP or community services). The comparator being assessed is FibroScan done in secondary or specialist care."
2*. The economic importance of the research question is stated.	¨	X	¨		However, implied through submission to NICE MTEP.
3*. The viewpoint(s) of the analysis are clearly stated and justified.	¨	¨	X		Perspective not explicitly declared, but Company reports including both NHS and PSS.
4*. The rationale for choosing alternative programmes or interventions compared is stated.	X	¨	¨		Company justifies selection of intervention and comparator as being in line with the published scope.
5*. The alternatives being compared are clearly described.	X	¨	¨		Intervention and comparator, plus contributing costs, are described in the Economic Submission.
6*. The form of economic evaluation used is stated.	X	¨	¨		Model identified as cost-consequences decision tree.
7*. The choice of form of economic evaluation is justified in relation to the questions addressed.	X	¨	¨		"Decision tree approach selected to describe the potential patient pathways." "The decision tree structure allows the comparison of performing this transient elastography outside secondary care compared to within secondary care by breaking down the process into binary decisions."
Data collection					
8*. The source(s) of effectiveness estimates used are stated.	X	¨	¨		Sources for all parameters are stated; no long-term outcomes included (assumption same between both arms and therefore deemed appropriate by EAC to exclude from modelling).
9. Details of the design and results of effectiveness study are given (if based on a single study).	¨	¨	X		Cost consequence framework. Model illustrated in excel (not Economic submission). Decision tree used to model patient pathways

Item	Judgement				EAC comment
	Yes	No	Not clear	Not appropriate	
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	¨	¨	X		Cost-consequence framework. Scan failure was derived from mean of clinical studies within Clinical Submission (calculation and raw data not reported within Economic submission, calculation not identified in Excel model).
11*. The primary outcome measure(s) for the economic evaluation are clearly stated.	X	¨	¨		Terminal nodes described in the Economic Submission (Table 4) are: behavioural intervention, no behavioural intervention, referral to hepatologist, missed diagnosis of liver disease, no liver disease.
12. Methods to value benefits are stated.	¨	¨	¨	X	N/A – Cost-consequence analysis
13. Details of the subjects from whom valuations were obtained were given.	X	¨	¨		Experts listed on page 38/50 of Economic Submission. Company state that the model underwent both conceptual and technical validation. “Conceptual validation was provided by comparison with the pathways described in the Southampton CCG pilot study and consultations with the internal Echosens clinical experts with experience of patient referral practiced in the UK.”
14. Productivity changes (if included) are reported separately.	¨	¨	¨	X	N/A (not included)
15. The relevance of productivity changes to the study question is discussed.	¨	¨	¨	X	N/A (not included)
16*. Quantities of resource use are reported separately from their unit costs.	X	¨	¨		Yes (e.g. 15 minutes of GP practice nurse with hourly rate reported separately). Costs derived from NHS Reference costs could have been more explicitly reported by stating the frequency/activity of use within the 2019/20 year.
17*. Methods for the estimation of quantities and unit costs are described.	¨	¨	X		EAC queried sources of costs with Company (EAC Correspondence Log, 2021). EAC concerned “double counting” due to the addition of staff time for performing FibroScan in secondary or specialist care to an HRG cost bundle. This would lead to over-estimate of cost of FibroScan when used in hospital setting (i.e. leading to a reduction in cost difference between non-hospital and hospital setting).
18*. Currency and price data are recorded.	X	¨	¨		All costs in submission and model reported in GBP, except the tornado diagram axis,

Item	Judgement				EAC comment
	Yes	No	Not clear	Not appropriate	
					which was reported in dollars (EAC believes this to be an error).
19*. Details of currency of price adjustments for inflation or currency conversion are given.	X	¨	-		Latest sources used (2019/20 NHS ref costs, 2020 PSSRU), all reported in £; therefore no need for inflation or conversion.
20. Details of any model used are given.	X	¨	¨	¨	"A decision tree approach was selected to describe the potential patient pathways." Illustration in Excel model (introduction worksheet).
21. The choice of model used and the key parameters on which it is based are justified.	X	¨	¨	¨	Choice of model and parameters supporting it are justified in the Economic Submission.
Analysis and interpretation of results					
22*. Time horizon of costs and benefits is stated.	X	¨	¨		Time horizon described as less than one year, with justification "Any difference between the arms in the model can be captured during the time the scans are performed and follow-up treatments are decided." Given the assumption that the same device is used in the same population, the EAC agrees that long-term outcomes would be the same between arms and therefore appropriate to simply and remove from the model when using a cost-consequences framework.
23. The discount rate(s) is stated.	X	¨	¨	¨	Discount rate reported as "None".
24. The choice of discount rate(s) is justified.	¨	¨	¨	X	
25. An explanation is given if costs and benefits are not discounted.	X	¨	¨	¨	"Due to the short time horizon, no discounting was necessary". The EAC considers this appropriate.
26. Details of statistical tests and confidence intervals are given for stochastic data.	X	¨	¨	¨	Only difference between arms reported. Confidence intervals reported for PSA.
27. The approach to sensitivity analysis is given.	X	¨	¨	¨	"Parameter uncertainty was assessed in the univariate (one-way) sensitivity analysis and probabilistic sensitivity analysis (PSA)." Subgroup analysis also reported (NAFLD, ALD, hepatitis). 1000 iterations included in PSA.
28. The choice of variables for sensitivity analysis is justified.	X	¨	¨	¨	All model parameters or composite pathways were varied.

Item	Judgement				EAC comment
	Yes	No	Not clear	Not appropriate	
29. The ranges over which the variables are varied are justified.	¨	¨	X	¨	"…each parameter was varied according to its 95% confidence internal (CI), while holding all other parameters constant. Where the published study or source for parameter values did not report standard errors or CIs, or patient counts which would have allowed calculation of CIs, 10% variation of the mean was assumed." Assuming only 10% variation of the mean may not include a plausible range of values. Costs also varied.
30. Relevant alternatives are compared.	X	¨	¨	¨	Only FibroScan in hospital setting compared with FibroScan in a non-hospital setting (in line with final scope (NICE, 2021).
31. Incremental analysis is reported.	¨	X	¨	¨	Univariate analysis reported using tornado diagram, then PSA (all parameters varied).
32*. Major outcomes are presented in a disaggregated as well as aggregated form.	X	¨	¨		Table 9 in Economic Submission reports the base case results as totals, and broken down into scan costs, missed appointment costs, hepatologist referral costs and behavioural intervention costs for both intervention and comparator.
33*. The answer to the study question is given.	X	¨	¨		"Despite the increase of cases identified, FibroScan used outside of secondary or specialist care reduces costs by reducing the number of visits to hepatologist departments as well as reducing the opportunity costs of missed scan appointments." "The incremental cost per patient of FibroScan outside secondary or specialist care is -£41.05 compared to the standard of using FibroScan in secondary care. This denotes cost savings."
34*. Conclusions follow from the data reported.	X	¨	¨		"Furthermore, Southampton CCG study reported increase in uptake of the FibroScan examination (a reduction from 21% to 8.6% of patients who failed to attend scans) from phase 1 to phase 2. The increase in uptake indicates increase in early identification and decrease in missed diagnosis of liver diseases. Cost of management of different liver disease stages reported by Crossan C et.al, 2015 shows increase in cost with the increase in severity of disease. For example- cost of management of mild fibrosis (cost in 2012) was £185 compared to the cost of liver transplantation (cost in 2012) which was £64,122. Hence, it can be inferred that in the long run early identification of disease

Item	Judgement				EAC comment
	Yes	No	Not clear	Not appropriate	
					will result in significant cost savings even over and above the savings captured in the current economic model through the reduced number of secondary or specialist care attendance."
35*. Conclusions are accompanied by the appropriate caveats.	X	¨	¨		Limitations reported as: "The analysis also relies on a pilot study testing the use of FibroScan in the Southampton CCG, therefore captures referral rates that represent a UK population. The model time horizon is short, and some of the longer terms benefits have not been captured in the calculations. However, there is strong evidence to support that earlier diagnosis is likely to lead to further cost savings. There is currently no subgroup-specific data on attendance rates for the scans nor on the proportion of patients requiring hepatologist referrals. The calculations can be updated when the subgroup-specific information from the Southampton CCG pilot study becomes available." Company acknowledges that the difference between attendance rates for the scans drives the model, yet the EAC notes that no published comparator data exists. Company acknowledges that magnitude of cost saving will depend on staff level used to perform the scan in primary care and time taken. EAC notes that there may be wide variability (which could be addressed in sensitivity analysis).

* *"Not appropriate"* is not considered an available option

Appendix E: Economic modelling conducted by the EAC

Appendix E1: EAC replication of Company model

FibroScan

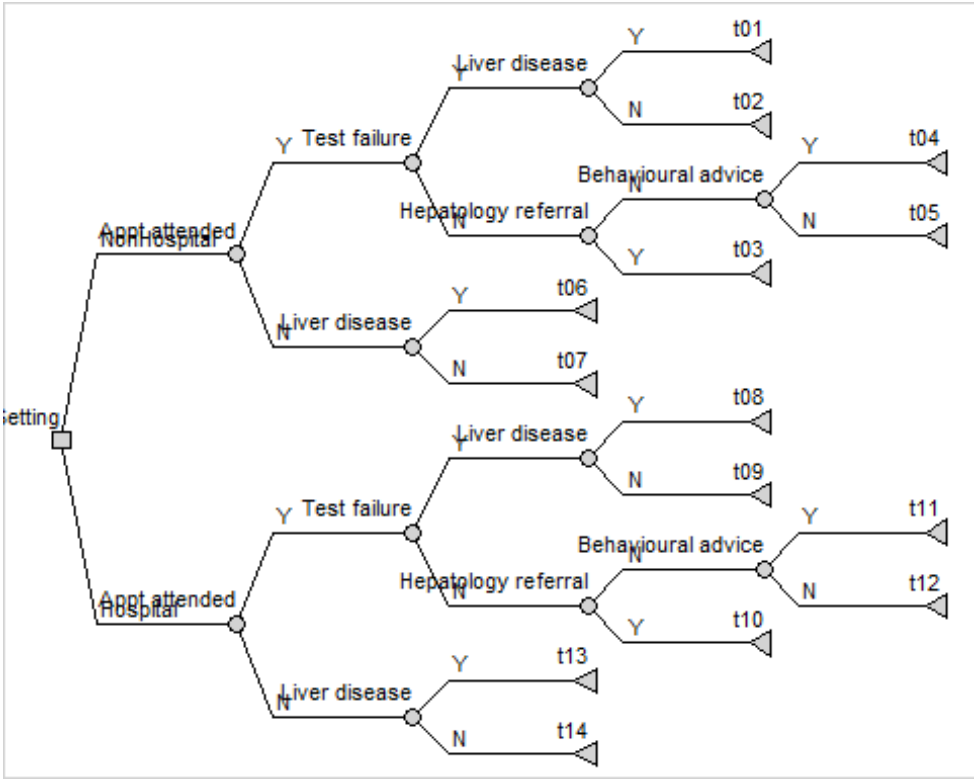
Kim Keltie, Andrew Sims

26/10/2021

Company's model

Decision tree structure

Figure 1: Decision tree for FibroScan (Company model)



Model variables

Probabilities at chance nodes were modelled with Beta distributions (Table 1) having point estimates and inter-quartile ranges as shown in Table 2.

Table 1. Beta distributions for probabilities at chance nodes

Description	Distribution
No liver disease	Be(505,405)
Referral hepatology	Be(126,407)

Test success non-hospital	Be(4.05,0.2131579)
Appt attendance non-hospital	Be(66,533)
Test success hospital	Be(4.05,0.2131579)
Appt non-attendance hospital	Be(79.8,319.2)

Table 2. Point estimates and IQR of probabilities at chance nodes

Variable	Mean	Q2.5	Q97.5
No liver disease,	0.555	0.523	0.587
Referral hepatology,	0.236	0.201	0.273
Test success non-hospital,	0.95	0.653	1
Appt attendance non-hospital,	0.11	0.0864	0.136
Test success hospital,	0.95	0.653	1
Appt non-attendance hospital,	0.2	0.162	0.241

Results

Base case

Base case, by path

For the purpose of checking, the probabilities and costs of each path in the model, assuming each variable takes the value of its point estimate, is shown in Table 3.

Table 3. Base case model details, by path.

Leaf	Setting	Probability	Cost
t01	NonHospital	0.02	1.59
t02	NonHospital	0.025	1.99
t03	NonHospital	0.2	57.62
t04	NonHospital	0.645	77.28
t05	NonHospital	0	0
t06	NonHospital	0.049	0.51
t07	NonHospital	0.061	0.64
t08	Hospital	0.018	2.44
t09	Hospital	0.022	3.04
t10	Hospital	0.18	54.23
t11	Hospital	0.58	102.34
t12	Hospital	0	0
t13	Hospital	0.089	8.29

t14	Hospital	0.111	10.34

Base case, by strategy

Results of the base case are shown in Table 4.

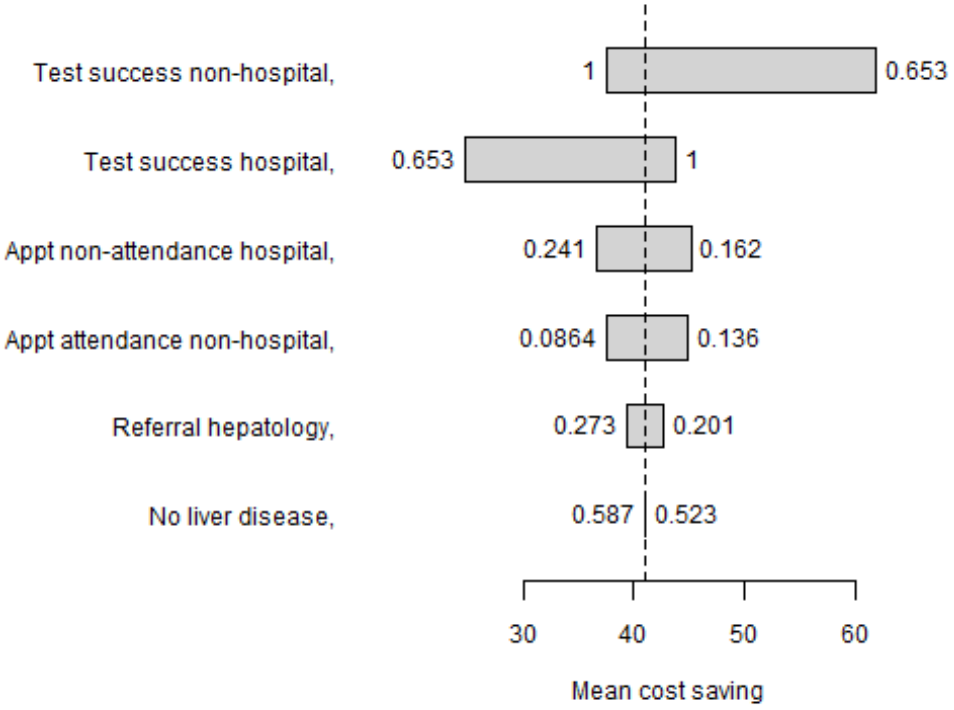
Table 4. Base case results

Setting	Cost
Hospital	180.7
NonHospital	139.65

Deterministic sensitivity analysis

Each model variable in turn was allowed to vary across its 95% confidence interval with the remainder set to their point estimates. The results are shown in the tornado diagram (Figure 2).

Figure 2: Tornado diagram for the FibroScan model



Probabilistic sensitivity analysis

In PSA, each variable was sampled from its uncertainty distribution for each run of the model (a multivariate simulation). The results of 1000 runs are shown in Table 5. Mean cost difference (NonHospital - Hospital) -£40.72 (95%CI -£60.97, -£24.85) [min -£80.77; max -£0.72]. A total of 1000 runs (100%) were cost saving.

Table 5: Example 10 runs from PSA

Run	Cost.NonHospital	Cost.Hospital	Difference
1	141	181.5	-40.47
2	147.6	186.2	-38.64
3	135.2	178	-42.78
4	146.5	187.5	-41.04
5	145	186.9	-41.87
6	140.6	180.7	-40.02
7	138.2	156.5	-18.29
8	146.3	186.2	-39.82
9	143.2	175.8	-32.6
10	128.3	177.4	-49.17

Appendix E2: EAC base case and sensitivity analyses

FibroScan EAC base case

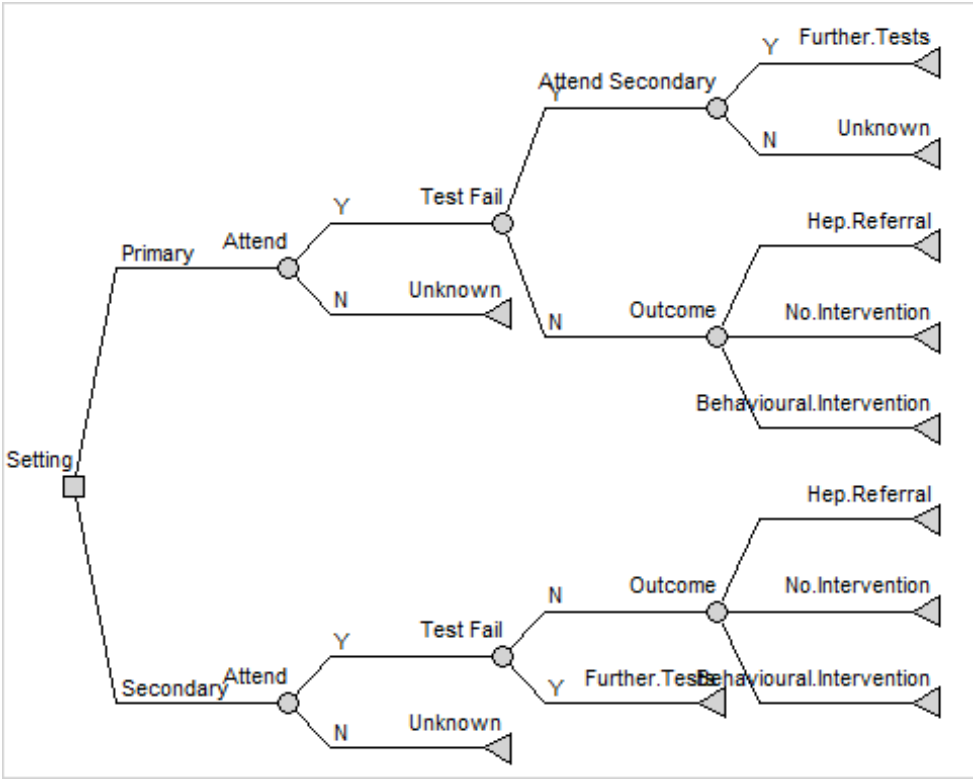
Kim Keltie, Andrew Sims, Rachel O'Leary

05/11/2021

Company's model

Decision tree structure

Figure 1: Decision tree for FibroScan (EAC base case model)



Model variables

Probabilities at chance nodes were modelled as constants, or with Beta distributions (Table 1) having point estimates and inter-quartile ranges as shown in Table 2.

Table 1. Distributions, point estimates and IQR of probabilities at chance nodes

Description	Distribution	Mean	Q2.5	Q97.5
Attendance rate (secondary)	Const(0.6)	0.6	0.6	0.6
Hepatology referral rate	Const(0.05925)	0.0593	0.0593	0.0593
Discharge with no intervention	Const(0.7692)	0.769	0.769	0.769
Test failure (both arms)	Be(64,855)	0.0696	0.0541	0.087

Attendance rate (primary)	Const(0.9)	0.9	0.9	0.9
Behavioural intervention rate	Const(0.1715)	0.172	0.172	0.172

Results

Base case

Base case, by path

For the purpose of checking, the probabilities and costs of each path in the model, assuming each variable takes the value of its point estimate, is shown in Table 3.

Table 3. Base case model details, by path

Leaf	Setting	Probability	Cost
Further.Tests	Primary	0.038	4.19
Unknown	Primary	0.025	2.79
Hep.Referral	Primary	0.05	13.66
No.Intervention	Primary	0.644	43.48
Unknown	Primary	0.1	6.75
Further.Tests	Secondary	0.042	3.67
Hep.Referral	Secondary	0.033	6.9
No.Intervention	Secondary	0.429	18.86
Unknown	Secondary	0.4	17.57
Behavioural.Intervention	Primary	0.144	9.69
Behavioural.Intervention	Secondary	0.096	4.21

Base case, by strategy

Results of the base case are shown in Table 4.

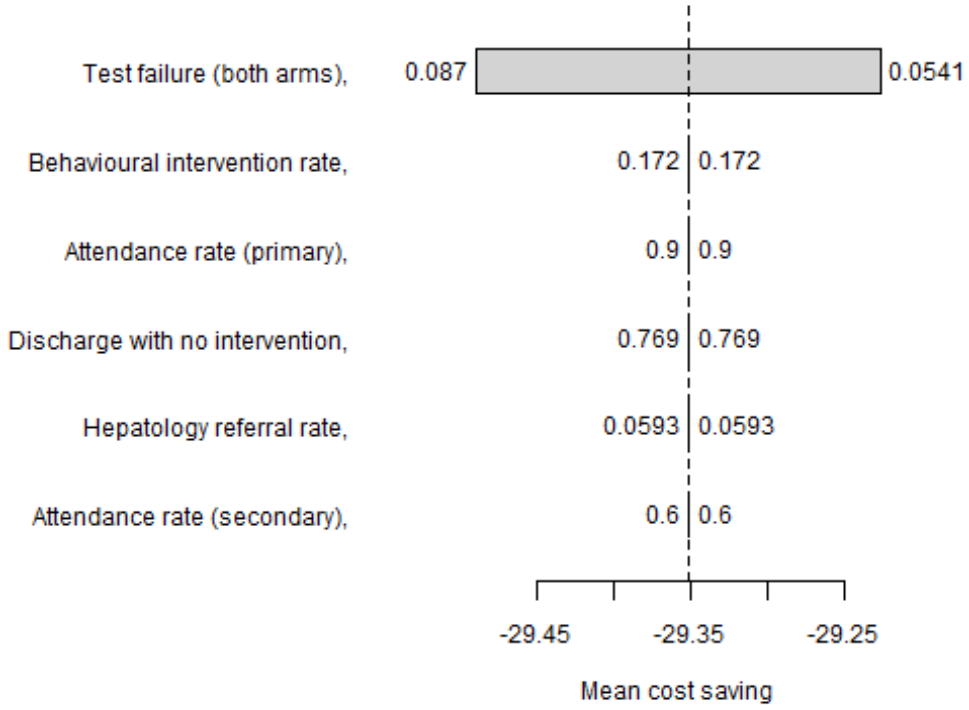
Table 4. Base case results

Outcome	Primary Care	Secondary Care
Total cost per patient (GBP)	80.57	51.21
Patients with unknown outcomes	125	400
Costs due to missed appointments (GBP)	2048.25	17572
Patients referred to hepatology	50	33

Deterministic sensitivity analysis

Each model variable in turn was allowed to vary across its 95% confidence interval with the remainder set to their point estimates. The results are shown in the tornado diagram (Figure 2).

Figure 1: Decision tree for FibroScan (EAC base case model)



Probabilistic sensitivity analysis

Table 5: Example 10 runs from PSA

Run	Cost.Primary	Cost.Secondary	Difference
1	80.6	51.24	29.36
2	80.87	51.44	29.44
3	80.35	51.06	29.29
4	80.55	51.2	29.35
5	80.46	51.14	29.32
6	80.79	51.38	29.41
7	80.31	51.03	29.28
8	80.52	51.18	29.34
9	80.77	51.36	29.41
10	80.69	51.3	29.38

In PSA, 1000 runs were completed and 10 are shown in Table 5. The mean cost difference between primary care and secondary care (that is, mean cost in primary care, minus mean cost in secondary care) was 29.36 GBP (95% CI 29.23 GBP to 29.5 GBP), ranging between 29.13GBP and 29.57GBP. A total of 0 measurements (0%) were cost saving.

Further sensitivity and scenario analyses

Sensitivity analysis

Two way sensitivity analysis for attendance rates

	0.37	0.47	0.57	0.67	0.77	0.87	0.97
0.9	24.9	25.26	25.62	25.98	26.33	26.69	27.05
0.8	25.35	25.83	26.31	26.79	27.27	27.75	28.23
0.7	25.8	26.4	27	27.6	28.2	28.81	29.41
0.6	26.25	26.97	27.69	28.42	29.14	29.86	30.59
0.5	26.7	27.54	28.38	29.23	30.07	30.92	31.76
0.4	27.14	28.11	29.08	30.04	31.01	31.98	32.94
0.3	27.59	28.68	29.77	30.86	31.94	33.03	34.12
0.2	28.04	29.25	30.46	31.67	32.88	34.09	35.3
0.1	28.49	29.82	31.15	32.48	33.81	35.14	36.47

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics guidance

Assessment report overview

FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care

This assessment report overview has been prepared by the Diagnostics Assessment Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Diagnostic Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations

1 The technology

FibroScan (Echosens) is a non-invasive medical device that assesses liver fibrosis and cirrhosis by measuring the degree of liver stiffness. It can distinguish normal liver or minimal fibrosis from cirrhotic livers. FibroScan uses proprietary vibration controlled transient elastography to quantify liver stiffness which is essentially a measure of the extent of liver scarring. The test takes around 15 minutes to complete and does not require visualisation of the liver or the use of anaesthetics. During the assessment, a probe is placed on the skin over the liver. The probe emits a shear wave that passes through the subcutaneous tissue into the liver. An algorithm analyses the returned wave to determine its speed in meters per sec (m/s) and the equivalent stiffness in kilopascals (kPa). In harder tissue shear waves propagate faster. The threshold used in clinical practice may depend on the underlying cause of liver disease. In addition to fibrosis, FibroScan can also assess levels of fat in the liver using a controlled attenuation parameter (CAP) tool.

Products in the FibroScan range are listed in Table 2 of the EAC assessment report. Different sizes (small, medium or extra-large) of probes are available. The device comes with a medium probe. Small and extra-large probes are optional extras. The extra-large probe is designed to enhance signal penetration through deeper tissues, reducing device failure rates in obese patients. The company state that there is no restriction on the use of any of the products in primary care.

No specialised equipment is required to use FibroScan in primary or community care, other than a clinic room and a patient couch or bed. Echosens provides on-site training to all clinical staff operating FibroScan. Clinical experts confirmed that anyone can be trained to use FibroScan, with users gaining proficiency very quickly. However, they also highlighted a learning curve to using the technology.

Transient elastography is mainly used in secondary care but has been used in a primary or community care setting. This assessment focuses on the use of the technology outside secondary and specialist care.

2 Proposed use of the technology

2.1 Disease or condition

Liver fibrosis is a condition of the liver that can progress into cirrhosis if not managed (see further details below). A common feature of all liver disease is that over time it can cause low grade chronic inflammation and scarring of the liver. Risk factors for liver disease include excess alcohol intake, diabetes, obesity and hepatitis B and C infection.

Liver fibrosis

Liver fibrosis occurs when persistent inflammation of the liver causes excessive scar tissue to build up in the organ and nearby blood vessels. The presence of scar tissue can impair overall liver function and limit blood flow which may lead to the death of liver cells. Advanced liver fibrosis can develop into cirrhosis, liver failure, and portal hypertension and may require liver transplantation. Liver fibrosis is caused by hepatitis, non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ARLD).

Cirrhosis

Cirrhosis is a late-stage liver disease that occurs when inflammation and fibrosis has spread throughout the liver and disrupts the shape and function of the liver. Cirrhosis usually develops silently following exposure to 1 or more risk factors such as alcohol misuse and hepatitis B or C which cause inflammation within the liver, or obesity. However, not everyone with inflammation of the liver will eventually develop cirrhosis. Untreated cirrhosis can cause liver failure, liver cancer or death.

Patient group

The population for the assessment of this technology is people with suspected or confirmed liver disease who would have a FibroScan to assess for liver fibrosis or cirrhosis as per current NHS practice. The assessment does not

focus on who should have the test, but where it should be done. Specific populations within the overall population that were assessed as subgroups included people with NAFLD, ARLD or hepatitis.

2.2 Current management

Currently, transient elastography (FibroScan) is predominantly used in secondary care. The NICE guideline on cirrhosis in over 16s recommends the use of transient elastography to diagnose cirrhosis in people with hepatitis C, high alcohol consumption, diagnosed ARLD, or NAFLD and advanced fibrosis.

The NICE guideline on Hepatitis B recommends transient elastography as an initial test for liver disease in adults newly referred for assessment and for the annual reassessment of liver disease in adults who are not taking antiviral treatment.

Although the NICE guideline on non-alcoholic fatty liver disease states that use of the enhanced liver fibrosis (ELF) test should be considered in people who have been diagnosed with NAFLD to test for advanced liver fibrosis, in clinical practice FibroScan is often used instead of, or alongside the ELF test. This is consistent with guidelines published by the British Society of Gastroenterology and the British Medical Journal.

2.3 Proposed management with new technology

The company proposes that Fibroscan could be used outside a secondary or specialist setting (for example, GP or community services). According to the scope of this guidance, this assessment will only consider FibroScan as currently used in the NHS (that is, not in a wider population or extent of use), but in use outside secondary and specialist care.

3 Company claimed benefits and the decision problem

The benefits to patients claimed by the company are:

- Enables earlier or more accurate diagnosis

- Reduces risks, side effects or complications
- Enables a test, procedure or treatment to be done non-invasively
- Enables behaviour changes or lifestyle interventions

The benefits to the healthcare system claimed by the company are:

- Enables delivery of care in primary care setting (e.g. GP or community services) rather than in secondary care setting.
- Increases compliance
- Requires less time
- Reduce unnecessary referrals to secondary care

Some of the benefits of FibroScan claimed by the company may include benefits that would only be realised from wider, or earlier, use of the technology. This usage is not evaluated in this assessment (see section 2.4).

The decision problem was described in the scope (see Appendix D). No variations were proposed by the company.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company submitted 7 publications it considered relevant to the decision problem in its clinical evidence submission. The EAC excluded 3 of these publications due to either not separating results by setting, or not separating results for FibroScan from other non-invasive tests (see Table 1). A further 15 publications were identified from the EAC's independent literature search, for a total of 19 publications included in the assessment report. Summary information on the included and excluded publications is in Table 1; further details can be found in section 4.2 of the EAC assessment report.

No evidence was identified which directly compared the use of FibroScan in primary or community care against its use in secondary or specialist care in line with the final scope.

Table 1: Publications included by the company and/or EAC

Study	Type of publication	Type of study	Comment
Publications included by both EAC and company			
El-Gohary et al. 2018	Full paper	Randomised controlled trial	
Harman et al. 2015, Harman et al. 2018, Harris et al. 2019	Full paper	Cross-sectional study	
Publications in company submission excluded by EAC			
Harris et al. 2017	Full paper	Systematic review	Intervention combined results from all non-invasive tests for liver fibrosis
Mansour et al. 2021	Full paper	Cohort study	Mixed setting, intervention and comparator results not reported separately
Rhodes et al. 2021	Full paper	Retrospective cross-sectional study	Setting out of scope – used in a tertiary centre
Publications not in company submission included by EAC			
Reinson et al. 2021	Full paper	Cohort study	Subgroup follow up from El-Gohary et al. 2018
Harris et al. 2018	Full paper	Prospective cross-sectional study	
Knight et al. 2020	Full paper	Qualitative study	
Matthews et al. 2019	Full paper	Prospective observational study	
Surey et al. 2019	Full paper	Observational study	
Corrigall et al. 2018, Hashim et al. 2019, O'Sullivan et al. 2019, Siu et al. 2019, Mohamed et al. 2020	Conference abstract	Cohort study	

Roberts et al. 2015, Hosack et al. 2019	Conference abstract	Prospective cohort study	
Irving et al. 2017	Conference abstract	Before-and-after study	
McGinley et al. 2017	Conference abstract	Retrospective observational study	
Montague et al. 2020	Conference abstract	Qualitative study	

The EAC only considered studies done in a UK setting as relevant for this assessment. The clinical evidence includes the LOCATE cluster randomised feasibility study (El-Gohary et al. 2018) which compared the use of targeted liver pathways in primary care against standard primary care, although only the intervention arm was used by the EAC in their assessment (see below). A long-term cohort follow up of a LOCATE subgroup (Reinson et al. 2021) was also identified and assessed by the EAC.

The EAC considered the LOCATE study to have a high risk of bias. Patient characteristics (age, gender, diabetes and alcohol use) were different between intervention and comparator centres, which the authors attributed to one centre having a high population of university students. In addition to use of FibroScan, the intervention arm used targeted screening and serum fibrosis markers not used in the control arm, therefore new cases of liver disease detected could not be solely attributed to the use of FibroScan.

The evidence base also includes various cross-sectional studies (Harman et al. 2015; Harman et al. 2018; Harris et al. 2018; Harris et al. 2019) and a qualitative study (Knight et al. 2020) from the Nottingham Community Liver Biomarkers Cohort Study, based in GP practices. The remaining publications and abstracts are for studies based in community drug or alcohol support settings, homeless day centres or hostels, or pop-up, community or GP clinics.

The EAC critically appraised cross-sectional studies and cohort studies using the corresponding STROBE checklists. The remaining 10 studies were only available in abstract form and the EAC did not critically appraise them.

However, these abstracts have been included in the assessment due to their value in reporting test failure, uptake, NHS resource use and morbidity outcomes. For further detail, see EAC assessment report Section 5.2 and Appendices B1 to 3.

Most evidence included in the assessment report used older models of FibroScan which are now no longer available, or did not report the model (with the exception of Reinson et al. 2021). The company have claimed equivalence in clinical, biological, and technical characteristics, and therefore equivalence of clinical evidence for all models of FibroScan.

The company also notified the EAC of a completed pilot study in the Southampton CCG for which results have not yet been published. However, interim results for scan attendance and referral to hepatology were used in the company's economic model (see Section 4.2).

Clinical evidence outcomes

Test failure

Test failure was consistently defined across five studies, as the inability to obtain ten valid measurements with the FibroScan device (which is in line with FibroScan instructions for use). Test failures for most studies were between 1.7% and 2.2%. Three studies (Harman et al. 2015, Harman et al. 2018, Harris et al. 2019) also reported on test unreliability, however the criteria for an unreliable test varied between studies (see EAC assessment report Table 10).

Test accuracy

No diagnostic accuracy studies for FibroScan outside of secondary or specialist care were identified, and no study reported on test agreement between FibroScan in secondary or specialist care and FibroScan outside secondary or specialist care.

Test uptake

Reported uptake of FibroScan (or additional healthcare visits including FibroScan) ranged between 36% and 97%. Although uptake for FibroScan in secondary care was not reported in the clinical evidence base, clinical experts advised that the "did not attend" rate is lower for FibroScan appointments in primary care (10%) when compared with FibroScan done in a hospital setting (40%).

Test outcome

Most studies reported the severity of liver fibrosis according to FibroScan results. Elevated liver stiffness was consistently reported as FibroScan measurements of 8 kPa and above, and ranged between 9.8% (El-Gohary et al. 2018) and 27% (McGinley et al. 2017). Probable cirrhosis was broadly defined as FibroScan measurements of 13 kPa or above. This ranged between 2.3% (El-Gohary et al. 2018) and 17% (Hashim et al. 2019). However, the method of confirmation of results was variable between studies. Review by or referral to a hepatologist was common, and in a few cases liver biopsy or gastroscopy was done. In the company's model, values for prevalence of liver disease were sourced from El-Gohary et al. (see Section 4.2 and Table 3 below).

Safety

No studies in the clinical evidence base reported on device-related adverse events or mortality. The EAC did not find any additional reports of adverse events in the published literature or in adverse event databases and were satisfied that there are no major safety concerns for the FibroScan device.

Meta-analysis

The company conducted meta-analysis combining the detection rate of advanced fibrosis reported by 6 studies (Mansour et al. 2021; Rhodes et al. 2021; Harris et al. 2019; El-Gohary et al. 2018; Harman et al. 2018; Harman et al. 2015). The EAC were unable to replicate the company's meta-analysis in R, but considered that the study heterogeneity was so great that meta-

analysis was not appropriate in this assessment (for further information see EAC assessment report Section 7).

Clinical evidence conclusions

The EAC concluded that the clinical evidence demonstrates that the FibroScan can be used across a range of settings (including GP practices, community clinics, drug or alcohol centres, homeless centres, mobile outreach services) with measurements taken by liver nurses and peer support workers. Clinical experts advised that local diagnosis is an additional benefit to patients (with fewer hospital visits and reduced wait times), with repeated measurements enabling ongoing monitoring in the community. FibroScan is not currently available across many regions of the UK. A recent survey (Jarvis et al. 2021) suggested that FibroScan is being used in 25% of CCGs.

The EAC examined the claimed benefits of FibroScan outside of secondary or specialist care made by the company in the context of the clinical evidence included (see EAC assessment report Table 3). The EAC considers there to be likely benefit in terms of earlier diagnosis and opportunity for behaviour or lifestyle change, largely due to the increased attendance rate for appointments outside of secondary care. However, the EAC was unclear as to whether FibroScan outside of secondary or specialist care would avoid unnecessary referrals to secondary care. Referral is highly dependent on local pathways, and would still be required in many cases (for example, elevated FibroScan score, test failure, unavailability of XL+ probes). The EAC also noted that no benefit was proven for more accurate diagnosis, fewer invasive procedures, or reduced risk of side effects or complications for FibroScan outside of secondary or specialist care.

Table 2: Pivotal studies of FibroScan outside secondary or specialist care

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Funding	Comments
El-Gohary et al. 2018 Randomised controlled trial	**Participants:** 53,074 eligible **Intervention:** 2082/26,838 invited, 910 attended liver clinic **Setting:** UK GP practice	**Intervention:** Nurse-led liver clinic including physical measurements, blood samples and FibroScan following three different referral pathways **Comparator:** Standard care	**Outcomes:** Attendance, proportion with liver disease. **Follow up:** Single visit.	**Attendance:** 910/2082 (43.7%) **Liver disease:** No fibrosis (<6 kPa): 505 (55%) Liver warning (6–8 kPa): 220 (24%) Progressive fibrosis (8–12.9 kPa): 131 (16%) Probable cirrhosis (≥13 kPa): 44 (5%)	British Liver Trust	As intervention included targeted screening approach as well as FibroScan use, detection of new cases of liver disease can not be solely attributed to FibroScan. Therefore, only results from intervention arm considered.
Reinson et al. 2021 Cohort study	Follow-up study of intervention arm from El-Gohary et al. 2018 116 eligible for rescan (out of 401 contacted)	Nurse-led community liver service; FibroScan used in n=59	Attendance at follow-up clinic, change in liver fibrosis stage. Single visit	**Attendance at follow up:** 59/116 (50.9%) **Change in liver fibrosis stage:** No change: 19 (32.2%) Decrease: 29 (49.1%) Significant change (F1 to F2): 2 (3.4%) Advanced change (F1/F2/F3 to F3/F4): 9 (15.3%) **Test failure:** 1 (1.7%)	British Liver Trust and Solent NHS Trust	Subgroup of El-Gohary et al. (2018) study. However provided long-term outcomes not captured elsewhere.

Matthews et al. 2019 Prospective observational study	**Population:** People over 16 attending a triage facility or currently undergoing alcohol support. N=79 **Setting:** Community alcohol support centre	Portable FibroScan	Acceptability of cirrhosis screening, onward referral to specialist liver services	**Referral to specialist services:** • No onward referral ≤7 kPa: 56/76 (74%) • Nurse-led liver clinic >7 kPa: 20/76 (26%) • Referred to hepatology ≥8 kPa: 12/76 (16%) **Fibrosis severity:** Warning (≥7.1 & <8 kPa): 8/76 (10.5%) Significant fibrosis (≥8 & <12.5 kPa): 7/76 (9.2%) Probable cirrhosis (≥12.5 kPa): 5 (6.6%) **Attendance at liver clinic:** 19/20 (95%) **Attendance at hepatology appt:** 11/12 (92%) **Attendance at ultrasound, CT or MRI:** 12/12 (100%)	NHS Lothian	
Roberts et al. 2015 Prospective cohort	**Population:** People with no history of liver disease referred due to alcohol-related risk factors, N=189 **Setting:** UK community clinic	FibroScan	Uptake, severity of liver fibrosis, referrals to hepatology, association between FibroScan measurements and AUDIT scores	**Test uptake:** 189/527 (35.9%) **Fibrosis severity:** <8 kPa: 146/182 8–12 kPa: 19/182 12–20 kPa: 10/182 >20 kPa 7/182	Not reported	Abstract only

Table abbreviations: AUDIT; alcohol use disorders identification test.

4.2 Summary of economic evidence

The company submission identified 4 studies in their economic submission. The EAC considered all 4 studies to have relevance to the decision problem and did not identify any additional published economic evidence done from a UK perspective. Only Crossan et al. (2019) directly compared costs of identical pathways between settings.

- Srivastava et al. (2019) presents a cost-comparison of 5 scenarios (of which 2 include FibroScan in primary care) using a probabilistic decisional model simulation (1000 simulated patients with confirmed NAFLD) from a UK NHS perspective. Scenario 3 (FIB-4 and FibroScan in primary care) had a cost-saving over 1 year of £151,816 for 1000 patients, compared to standard care (routine blood tests and ultrasound in primary care), while FibroScan in primary care alone (scenario 5) had a total cost saving of £26,889. The main contributor to the saving was a reduction of secondary care referrals.

- Tanajewski et al. (2017) presents a cost-effectiveness evaluation of a risk stratification pathway in which people at high risk of developing liver disease are offered community-based FibroScan. The standard care comparator consisted of liver function tests (LFTs), followed by referral to secondary care in case of persistently abnormal LFTs after 6 months. A decision tree and Markov model were used, informed by a feasibility study of 293 people with risk factors for chronic liver disease, and the evaluation was from a UK NHS perspective. The mean lifetime cost per patient of the risk stratification pathway was an additional £512 compared to standard care using deterministic cost-effectiveness analysis, and £225 using probabilistic analysis. The EAC commented that the comparative cost had wide confidence intervals and the confidence interval for the cost difference crosses zero.

- Crossan et al. (2019) presents a cost-calculator of 3 scenarios for people with NAFLD being tested for advanced fibrosis, of which 1

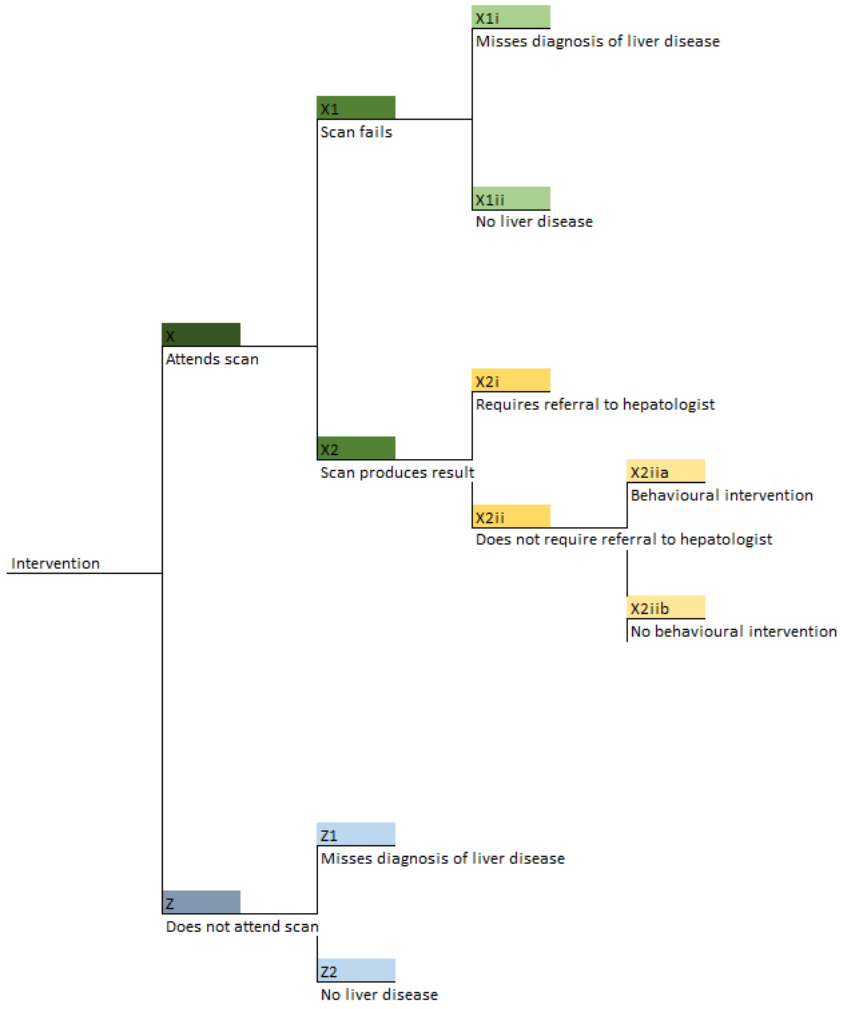
includes FibroScan in primary care. The perspective is assumed to be that of the UK NHS, over a time horizon of 5 years. At a 5% prevalence of advanced fibrosis, the mean total cost per person for the FibroScan in primary care scenario was £963 without liver biopsy for people with advanced fibrosis (as assessed by non-invasive testing) or above, or £839 with liver biopsy for people with advanced fibrosis or above, compared with £1,100 for the scenario in which all patients were referred to tertiary care (in which FibroScan was a possible test).

De novo analysis

The company developed a de novo cost consequences model in Excel, comparing the use of FibroScan outside of secondary of specialist care with its use in secondary or specialist care over a 1-year time horizon. None of the previously identified economic studies were used to inform the model.

The model consisted of a single decision tree, following a patient from the time a decision is made to do FibroScan (based on FIB-4 results) through testing in either setting. The structure of each arm is identical, with patients either attending or not attending the scan. For patients who do not attend their FibroScan appointment, their pathway ends with either no liver disease or a missed diagnosis of liver disease. These same endpoints are reached if the patient attends for FibroScan, but the scan fails and no result is available. If a result is produced, the patient is either referred to a hepatologist, has a behavioural intervention or has no further management. The structure of the model is shown in Figure 1. The model is capable of subgroup analysis based on liver condition (NAFLD, ARLD or hepatitis infection) by adjusting for the prevalence of that condition and likelihood of requiring a referral to hepatology.

Figure 1: Structure of the de novo economic model (taken from company model)



The EAC considers the approach taken by the company to be appropriate regarding population, time horizon, intervention and comparator, and outcomes. However, the EAC considered that the pathway should have incorporated follow-up appointments in secondary care in cases of a failed reading done outside secondary or specialist care. The EAC also noted that because there are no further costs for people who do not attend scans, and that people who attend scans can incur further costs, lower attendance leads to increased cost savings (in both arms). Additionally, there is no consequence of undiagnosed liver disease for those who do not attend their scan. Further exploration of the company model can be found in Table 22 of the EAC assessment report.

Model assumptions

The model makes a number of assumptions which can be seen in section 9.2 of the assessment report. Key assumptions are discussed below:

- The proportion requiring referral to a hepatologist after a FibroScan test is assumed to be the same regardless of whether the scan is received inside or outside of secondary or specialist care.

- The proportion of failed scans is assumed to be the same regardless of location. The EAC considers this appropriate provided that the trained and competent user has access to the same device and probes and performs enough scans to maintain their skills. However, the EAC raised concerns that the level of adoption needed to maintain user skills outside of secondary or specialist care may be higher than current usage and could lead to a broadening of referral criteria, which is not accounted for in the model.

- In the case of a failed scan, diagnosis is assumed to be missed and the underlying disease will remain untreated. The EAC considers this assumption inappropriate, as clinical experts indicated that a failed FibroScan in primary care would be an indication for a follow-up appointment in secondary or specialist care.

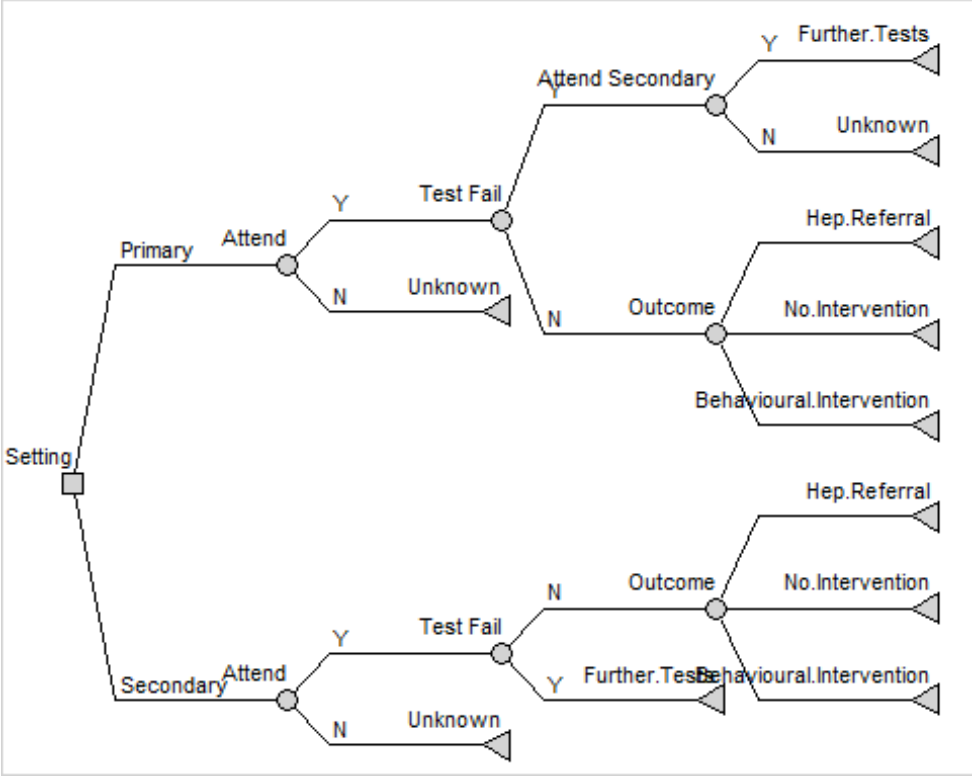
- The model assumes that FibroScan has maximum sensitivity and specificity, and there are no false positives or false negatives. The EAC considers this assumption appropriate as the true accuracy rates are unknown and modelling this would introduce further uncertainty. Experts advised that the risks of incorrect treatment following a false outcome are low.

EAC model

The EAC made changes to the company's model structure as shown in Figure 2. A branch was added for follow up after a failed test as per the above discussion, in which the patient would be referred to secondary care for further tests, or have additional tests if already in secondary or specialist care.

Additional testing was assumed to be liver ultrasound/elastography in secondary or specialist care. The EAC also assumed that additional appointments carried a risk of non-attendance at the same rate as the initial secondary or specialist care appointments. Presence of liver disease in those who did not attend a scan was assumed to remain unknown. Model parameters were also varied in the EAC's base case (described below).

Figure 2: Model structure of EAC base-case



Model parameters

Clinical parameters

A full description of the clinical parameters used in the company's model and comments made by the EAC are in Table 17 of the EAC assessment report. A summary is presented in Table 3:

Table 3: Clinical parameters used in the company's model and adjustments by the EAC

Parameter	Value used in submission	Source	Value used in EAC base case	EAC comments
Does not attend scan (outside of secondary or specialist care)	11%	Southampton CCG	11%	Variation in published literature addressed in sensitivity analysis (2-way deterministic analysis, see EAC assessment report Table 24)
Does not attend scan (secondary or specialist care)	20%	Southampton CCG	40%	EAC value obtained from clinical expert advice. Uncertainty addressed in sensitivity analysis (2-way deterministic analysis, see EAC assessment report Table 24)
Scan produces a result	95%	Assumption	93%	EAC value combines both test failure and test unreliability, based on values from literature
No liver disease	55%	El-Gohary et al. 2018	76.9%	El-Gohary et al. use a threshold of 6 kPa to determine presence of liver disease. However, in most studies, and in clinical practice, a threshold of 8 kPa is more commonly used. Thresholds are examined in scenario analyses. Additionally, the EAC used a three-tiered threshold approach (see below).
Requires referral to hepatologist	23.6%	Southampton CCG	5.9%	The EAC recommended a three-tiered threshold approach, in line with the pathway described by Chalmers et al. (2019), based on liver stiffness: - <8 kPa: no further referrals/investigations - Between 8.0 kPa and 14.9 kPa: provide behavioural advice, repeat 3-5 years - ≥15 kPa: refer to hepatology
Behavioural intervention	100%	Assumption	17.2%	See above

Table abbreviations: CCG, clinical commissioning group; EAC, external assessment centre

Costs and resource use

A full description of the cost parameters used in the company's model and comments made by the EAC are in Table 18 of the EAC assessment report. A summary is presented in Table 4.

In the company's base case, the cost of a FibroScan (including staff time) was £137.12 in secondary or specialist care and £80.50 if done outside this setting. In the EAC's base case this was amended to £43.93 for FibroScan in secondary or specialist care and £67.50 outside this setting. The main drivers of these changes are that the company's model uses a cost of £70.00 for a FibroScan outside of secondary or specialist care, however in later correspondence it was confirmed that this was an error, and as such the updated cost of £58.00 was used in the EAC's model. The EAC also noted that the cost of FibroScan in secondary or specialist care used in the company's submission double-counted staff time to perform and evaluate the scan, which was included in the HRG code assumed by the company to only include the cost of FibroScan. An additional cost of £93.19 per scan to perform and evaluate scan in secondary or specialist care included by the company was therefore omitted by the EAC.

Table 4: Cost parameters used in the company's model and adjustments by the EAC

Item	Cost used in submission	Source	Cost used in EAC base case	EAC comments
FibroScan GO (230) – Pay Per Exam outside of secondary/specialist care	£70.00	Company submission	£58.00	Company confirmed error in economic model
15 minutes of staff time to perform and evaluate scan outside of secondary or specialist care	£42.00 per hour	PSSRU Unit Costs of Health and Social Care 2020 Nurse (GP practice) including qualification costs	£38.00 per hour	The EAC excluded qualification costs in its base case as FibroScan does not require nursing qualifications
Cost of FibroScan in secondary or specialist care	£43.93	National Schedule of NHS costs 2019-20 IMAGOP RD48Z; Ultrasound Elastography	£43.93	The EAC increased cost to £61.98 in scenario analysis to account for 2019-20 actual usage
Staff time to perform and evaluate scan in secondary or specialist care	£93.19	National Schedule of NHS costs 2019-20 306 Hepatology WF01B; Non-Admitted Face-to-Face Attendance, First (Non-Consultant led)	£0.00	The EAC noted that staff time to perform and evaluate scan is already included in the HRG bundled cost above (RD48Z) and therefore this cost was removed to avoid double counting
Cost of missed appointment in secondary or specialist care	£93.19	National Schedule of NHS costs 2019-20 306 Hepatology WF01B; Non-Admitted Face-to-Face Attendance, First (Non-Consultant led)	£93.19	The EAC noted that the company model did not include costs of missed appointments outside of secondary and specialist care, and in its base case assumed that the cost of a missed appointment there would be the same as if the appointment had been attended. This was examined further in scenario analyses.

Referral to hepatologist from outside of secondary or specialist care	£207.86	National Schedule of NHS costs 2019-20 306 Hepatology WF01B; Non-Admitted Face-to-Face Attendance, First (Consultant led)	£207.86	
Follow-up visit to hepatologist after scan in secondary or specialist care	£164.75	National Schedule of NHS costs 2019-20 306 Hepatology WF01B; Non-Admitted Face-to-Face Attendance, First (Consultant led)	£164.75	
GP consultation	£39.23	PSSRU Unit Costs of Health and Social Care 2020 General practitioner per patient contact lasting 9.22 minutes incl. qualification costs	£39.23	

Table abbreviations: Abbreviations: EAC, external assessment centre; HRG, Health Resource Group; PSSRU, Personal Social Services Research Unit

Results

Company base case results

The company's base case showed the use of FibroScan outside of secondary or specialist care to be cost saving compared to its use in secondary or specialist care. There was a cost saving of £41.05 (95% CI £12.66 to £71.44) per patient over a 1 year time horizon, driven by reduction in scanning costs and cost of missed appointments when using FibroScan outside of a hospital setting (Table 5). There was an increase in the number of referrals to hepatology or behavioural interventions and fewer missed diagnoses of liver disease when FibroScan was done outside of secondary or specialist care.

Table 5: Summary of base case results

Company estimate	**FibroScan outside of secondary or specialist care**	**FibroScan in secondary or specialist care**	**Difference (Outside of secondary or specialist care minus within secondary or specialist care)**
Costs	–	–	–
Scan costs	£71.63	£109.70	-£38.06
Missed appointment costs	£1.16	£18.64	-£17.48
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£25.32	£22.77	£2.56
Total cost (per patient)	**£139.65**	**£180.71**	**-£41.05**
Resource use (per patient)	**–**	**–**	**–**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.07	0.11	-0.04
Total number of visits to hepatology department	0.20	0.98	-0.74

Corrections were made by the EAC to the total cost per patient for FibroScan in secondary or specialist care (£180.71 from £180.57), and to the total number of visits to the hepatology department for FibroScan in secondary or specialist care (0.98 from 0.94), as failed scans in secondary or specialist care had not been counted in the company submission.

Sensitivity analyses

In the company's univariate deterministic sensitivity analysis, all results showed the use of FibroScan outside of secondary or specialist care to be cost saving, when compared to its use in secondary or specialist care. The result was most sensitive to changes in the scanning costs in secondary or specialist care, followed by the scanning costs outside of secondary or specialist care.

The company's probabilistic sensitivity analysis found the use of FibroScan outside of secondary or specialist care to be cost incurring in only 0.3% of simulations, with a mean difference in cost per patient between FibroScan outside of secondary or specialist care, and FibroScan in secondary or specialist care of -£41.44 (95% CI -£12.66 to -£71.44).

The company reported separate results for subgroups based on the underlying liver condition. All subgroup analyses found that FibroScan outside of secondary or specialist care was cost saving when compared to its use in that setting (people with NAFLD: −£41.03; people with ARLD: −£42.62; people with hepatitis: −£29.96). For further detail see section 9.3 of the EAC assessment report.

The EAC explored the company model further by changing various parameters (see EAC assessment report Table 22). All amendments the EAC made to the company model maintained a cost-saving outcome, with the exception of removing double-counting of staff time costs in secondary or specialist care. This amendment changed the total cost per patient outside of secondary or specialist care versus within that setting from cost saving to cost incurring (+£41.46).

EAC base case results

Under the EAC's base case, use of FibroScan outside of secondary or specialist care was cost incurring compared to FibroScan in that setting by £29.36 per patient (Table 6). However, FibroScan outside of secondary or specialist care was found to decrease the costs of missed appointments and the number of people who did not attend scans (and therefore have unknown outcomes), and increase referrals to hepatology, the potential benefits of which are not accounted for in the model.

Table 6: EAC base case results

	FibroScan outside of secondary or specialist care	FibroScan in secondary or specialist care	Difference (Outside of secondary care minus within secondary care)
Total cost per patient	**£80.57**	**£51.21**	**£29.36**
Patients with unknown outcomes per 1000 patients	125	400	−275
Costs due to missed appointments per patient	£2.05	£17.57	−£15.52
Patients referred to hepatology per 1000 patients	50	33	17

EAC sensitivity and scenario analyses

The EAC commented that a lack of robust published data meant that only the probability of test failure could be varied within 1-way deterministic and probabilistic sensitivity analyses in the EAC model (EAC assessment report Section 9.3). Two-way deterministic sensitivity analysis was done to assess the range of attendance proportions in primary care reported in the clinical literature (37% to 97%), and varying attendance in secondary care relative to this (10% to 90% of attendance outside this setting, EAC assessment report Table 24). The use of FibroScan in primary care was not found to be cost saving under any combination of attendance in primary care and relative attendance in secondary care.

To account for the large uncertainties present in the model, a range of scenario analyses were done by the EAC. Based on advice from clinical experts, the EAC examined the impact of delivering behavioural interventions in the same appointment as FibroScan, or as separate appointments in the same setting as the FibroScan test. For the base case referral proportions only, the EAC also considered that, in secondary care, the follow up for behavioural intervention may be given by a telephone call. In separate scenarios, the EAC varied proportions being referred to hepatology, for behavioural interventions, or for no further management, and proportion of failed tests in both settings and outside of secondary care only. None of these scenarios were found to be cost saving (EAC assessment report, Table 25).

The EAC considered threshold analysis, in which the cost per FibroScan in primary care was varied to identify the point at which its use in primary care became cost neutral in the EAC's base case. The EAC found the threshold below which the use of FibroScan outside secondary or specialist care becomes cost saving is £28.50 (EAC assessment report, Table 26).

5 Ongoing research

The EAC identified a single ongoing study in the UK examining the effect of FibroScan in combination with videos of recovery stories on drinking behaviour in people at risk of alcohol misuse. FibroScan will be done in GP practices. The study is expected to recruit 120 participants and is estimated to complete in November 2022. Primary outcomes include recruitment rate, retention rate, acceptability of the intervention and feasibility of outcome measures, while secondary outcomes address the extent of alcohol intake or misuse. Clinical experts also identified the Scarred Liver Project and ID-LIVER programmes. Further details can be found in the EAC assessment report section 8.2 and Appendix C.

6 Issues for consideration by the Committee

Clinical evidence

- There are currently no studies comparing the performance of FibroScan when done outside a secondary or specialist care setting with FibroScan done in this setting. The EAC commented that a study examining the accuracy of FibroScan by setting against the gold standard of liver biopsy is likely to be unethical, and suggest a cohort study in which eligible patients have FibroScan both in primary and secondary care (with blinding), to directly address the decision problem.

- In the reviewed literature, attendance for FibroScan (or additional healthcare visits including FibroScan) outside of secondary or specialist care ranged between 36% and 97%. Although uptake for FibroScan in secondary care was not reported in the clinical evidence base, clinical experts advised that attendance rate is higher for FibroScan in primary care when compared with FibroScan conducted in a hospital setting.

- Clinical experts advised that, given sufficient experience, there should be no difference in accuracy or failure rate based on setting. However, experts did highlight a learning curve with the technology, and that FibroScan would have to be done with sufficient frequency to maintain competence (see below). Clinical experts considered the potential consequences of false diagnosis based on FibroScan results, and commented that the risks are likely to be low. At-risk patients who receive a false negative result would undergo regular review, while false positives would likely result in lifestyle interventions to support weight loss or reduce drinking, which are not harmful.

- In this assessment, the use of FibroScan was assessed in the same population regardless of test location. However, the EAC commented that it is plausible that if FibroScan was more readily available in primary care that GPs may choose to use it in broader populations.

Cost evidence

- The difference in cost per patient for FibroScan done in secondary or specialist care between the company and EAC models is due to the removal of a separate cost for staff time in the company's model. This change makes the cost per scan for FibroScan outside of secondary or specialist care more expensive than use within these settings. The EAC's rationale for this change in their model is that the staff time cost is included in the HRG code for the cost of the scan itself within secondary or specialist care. If this change is also made in the company's model, the result becomes cost incurring.

- The EAC considered that the company's model omitted referral to secondary or specialist care in the case of a failed FibroScan reading, and added this pathway to their model. This change was based on advice from clinical experts.

- In both the company and EAC models, an increase in the number of people attending a FibroScan appointment if done outside secondary or specialist care leads to an increase in costs. This is driven by the increased number of people with liver disease who are subsequently referred to hepatology or behavioural intervention. Any impact of this (beyond immediate cost of hepatology referral or behavioural intervention) is not captured in the model.

- The EAC highlighted that neither the company's model nor the EAC's model consider:

    - The opportunity costs associated with the current service model of delivering FibroScan in secondary care,

    - Efficiency gains and improved service resilience arising from delivering FibroScan tests in a community diagnostic hub setting (either via a pay-per-use model or a capital purchase model),

    - Increased utility associated with referring more people to lifestyle intervention programmes.

- Any benefit to patients of scans being available outside secondary or specialist care was not included in the model. Clinical experts advised that local diagnosis is an additional benefit to patients (with fewer hospital visits and reduced wait times), with repeated measurements enabling ongoing monitoring in the community.

- Under the company's 'cost per scan' approach used in the model for FibroScan outside secondary or specialist care, the cost per scan outside of secondary care is £58, with a minimum of 25 scans per month and a minimum contract term of 36 months. The EAC commented that this approach may require wider use than covered by the scope of this assessment to avoid paying for unused scans. From NHS Reference Costs, a total of 3,561 ultrasound elastography investigations were conducted in outpatients in 2019/20. Only 12 non-hospital centres would be required (at 25 per month) to achieve 3,561 scans in a 12-month period. More scans per month may also be required to maintain technical competence in the NHS staff using FibroScan. The EAC commented that implementation in community diagnostic hubs may be a suitable approach to address this issue.

7 Authors

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Thomas Walker, Technical Adviser

NICE Diagnostics Assessment Programme

November 2021

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Keltie K et al. FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care, November 2021

B Submissions from the following sponsors:

- Echosens

C Related NICE guidance

- Hepatitis B (chronic): diagnosis and management. NICE clinical guideline CG165 (2017). Available from www.nice.org.uk/guidance/CG165
- Cirrhosis in over 16s: assessment and management. NICE guideline NG50 (2016). Available from https://www.nice.org.uk/guidance/ng50
- Non-alcoholic fatty liver disease (NAFLD): assessment and management. NICE guideline NG49 (2016). Available from https://www.nice.org.uk/guidance/ng49

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Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Janisha Patel

Consultant Hepatologist, University Hospital Southampton

Dr Deepak Joshi

Consultant Hepatologist, King's College Hospital, NHS Foundation Trust

Louise Campbell

Clinical Director, Tawazun Health

Prof Neil Guha

Professor of Hepatology, University of Nottingham

Dr Stephen Ryder

Consultant physician in hepatology and gastroenterology, Queens Medical Centre, Nottingham

Dr Ashis Mukhopadhya

Consultant Gastroenterologist and Hepatologist, Aberdeen Royal Infirmary

Dr Coral Hollywood

Consultant hepatologist, Gloucestershire Hospitals NHS Foundation Trust

Prof Michael Moore

Professor of Primary Care Research, University of Southampton

Dr Helen Jarvis

GP Partner, NIHR clinical doctoral research fellow, Newcastle University

Please see the EAC correspondence log for full details.

Appendix C: Comments from patient organisations

No advice or information was sought from patient and carer organisations.

Appendix D: decision problem from scope

Population	People having a FibroScan to assess for liver fibrosis or cirrhosis (as per current NHS practice)
Intervention	FibroScan done outside secondary or specialist care (for example, GP or community services).
Comparator	FibroScan done in secondary or specialist care
Outcomes	The outcome measures to consider include: • Test accuracy • Agreement between measurement made by FibroScan done in primary and secondary/tertiary care • Comparative performance between different FibroScan models • Test failure • Uptake of offered FibroScan test • Uptake of behavior/ lifestyle change intervention • Number of referrals to secondary care • Number of people referred to alcohol or weight management services • Severity of liver fibrosis • Device-related adverse events • Use of NHS services (for example, GP or outpatient appointments) • Mortality • Morbidity (such as liver cirrhosis, liver related complications, cardiovascular complications)
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	Use of FibroScan in specific populations, for example for people with: • Non-alcoholic fatty liver disease • Suspected non-alcoholic fatty liver disease (for example, people with metabolic syndrome or type-2 diabetes) • Alcohol-related liver disease • Suspected alcohol-related liver disease (for example, based on hazardous alcohol use)

	• Hepatitis	
Special considerations, including those related to equality	FibroScan may have higher failure rates in people with higher BMI, particularly for people with central obesity, where possible data reporting failure rates in this group should be extracted. People from Black African, African Caribbean and South Asian (Indian, Pakistani, Bangladeshi) backgrounds are at a higher risk of developing type 2 diabetes from a younger age and therefore have a higher risk of liver disease. People with alcohol or substance misuse are at higher risk of liver disease. Liver cirrhosis may in the long term, prevent a person from performing their normal day-to-day activities. Disability is a protected characteristic under the Equality Act 2010.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care

1 Technology

1.1 Description of the technology

FibroScan (Echosens) is a non-invasive medical device that assesses liver fibrosis and cirrhosis by measuring the degree of liver stiffness. It can distinguish normal liver or minimal fibrosis from cirrhotic livers. FibroScan uses proprietary vibration controlled transient elastography to quantify liver stiffness which is essentially a measure of the extent of liver scarring. The test takes around 15 minutes to complete and does not require visualisation of the liver or the use of anaesthetics. During the assessment, a probe is placed on the skin over the liver. The probe emits a shear wave that passes through the subcutaneous tissue into the liver. An algorithm analyses the returned wave to determine its speed in meters per sec (m/s) and the equivalent stiffness in kilopascals (kPa). In harder tissue shear waves propagate faster. FibroScan can measure liver stiffness up to 75kPa. The threshold used in clinical practice may depend on the underlying cause of liver disease.

FibroScan results can be combined with other parameters (including blood markers such as AST) to generate FibroScan-based scores.

In addition to fibrosis, FibroScan can also assess levels of fat in the liver using a controlled attenuation parameter (CAP) tool. From 2021, functionality is available to allow continuous measurement of CAP during an examination

using the SmartExam tool. Adding the SmartExam functionality is optional and comes at an extra cost.

Products in the FibroScan range are listed in table 1. Different sizes (small, medium or extra-large) of probes are available. The device comes with a medium probe. Small and extra-large probes are optional extras. The extra-large probe is designed to enhance signal penetration through deeper tissues, reducing device failure rates in obese patients. The company states that the Fibroscan 430 Mini and Fibroscan 430 Mini+ are currently used in primary care, noting that the greater mobility of these systems allows easier movement between different locations within the same primary care network. The company state that there is no restriction on the use of any of the products in primary care.

Table 1. Fibroscan products

Technology	Portable system	Smart Exam	Indications	Battery-powered	Weight (Kg)
FibroScan 230 / FibroScan Go (*The company states that Fibroscan 230 will be launched in the UK in 2022*)	Mobile	Yes	Liver fibrosis and liver steatosis	No	4.4
FibroScan 430 Mini and M probe (*The company states that Fibroscan 430 mini will not be sold form January 2022*)	Mobile	No	Liver fibrosis	Yes	5
FibroScan 430 Mini+ and M probe	Mobile	Yes	Liver fibrosis and liver steatosis	Yes	5

FibroScan 530 Compact and M probe	Transportable	Yes	Liver fibrosis and liver steatosis	Yes	10
FibroScan 630 Expert Spleen Pack and M probe	No	Yes	Liver fibrosis, liver steatosis and portal hypertension	No	46

Transient elastography is mainly used in secondary care but has been used in a primary care setting at some sites. This scope focuses on the use of the technology outside secondary and specialist care. Primary care services are the first point of contact to the NHS and includes general practice, community pharmacy, dental, and optometry (eye health) services. Community health services include district nursing and health visiting. This technology may also be used in community based services such as weight management services for obese people and alcohol support services alongside other community based services.

1.2 Relevant diseases and conditions

Liver fibrosis is a condition of the liver that can progress into cirrhosis if not managed (see further details below). It is estimated that every day in the UK, 40 people die from liver disease, making it the third leading cause of premature death in the UK (British Liver Trust). A common feature of all liver disease is that over time it can cause low grade chronic inflammation and scarring of the liver. Common risk factors for liver disease include excess alcohol intake, diabetes, obesity and hepatitis B and C infection.

Liver fibrosis

Liver fibrosis occurs when persistent inflammation of the liver causes excessive scar tissue to build up in the organ and nearby blood vessels. The presence of scar tissues can impair the overall liver function and limit blood flow which may lead to the death of liver cells. Advanced liver fibrosis can

develop into cirrhosis, liver failure, and portal hypertension and may require liver transplantation. Liver fibrosis is caused by the following liver diseases:

- Hepatitis – this refers to the inflammation of the liver caused by viral infection or excess alcohol consumption. There are several types of viral hepatitis including hepatitis A, B, C, D and E. Other types of hepatitis include alcoholic and autoimmune hepatitis. Hepatitis C is the most common viral hepatitis in the UK, and it is estimated that around 400,000 people are infected and 180,000 people in the UK have hepatitis B (British Liver Trust). Other forms of viral hepatitis are less common in the UK.

- Non-alcoholic fatty liver disease (NAFLD) – this is the most common cause of liver fibrosis. It starts as a simple fatty liver (steatosis) and can then progress to non-alcoholic steatohepatitis (NASH), a more severe form of NAFLD, estimated to affect up 5% of the UK population. Persistent NASH develops into fibrosis.

- Alcohol-related liver disease (ARLD) – this refers to the damage of the liver caused by excess alcohol intake. ARLD occurs in 3 stages, the first being alcoholic fatty liver disease, caused by intake of alcohol over a short period. It is reversible if alcohol intake is stopped. The second stage is alcoholic hepatitis which is caused by excess alcohol intake over a longer period. Cirrhosis is the third stage of ARLD (NHS 2018). ARLD is common in the UK and over the last few decades, the number of people with the condition has increased. Around 7,700 people die from ARLD each year (British Liver Trust).

Cirrhosis

Cirrhosis is a late-stage liver disease that occurs when inflammation and fibrosis has spread throughout the liver and disrupts the shape, repair and function of the liver. It is characterised by the replacement of normal healthy liver tissue with scar tissues and irregular bumps which harden and prevent the liver from functioning as normal. Cirrhosis usually develops silently

following exposure to 1 or more risk factors such as alcohol misuse and hepatitis B or C which cause inflammation within the liver, or in those individuals with non-alcoholic fatty liver disease (NAFLD). However, not everyone with inflammation of the liver will eventually develop cirrhosis. Untreated cirrhosis can cause liver failure, liver cancer or death. It is estimated that over 4,000 people in the UK die from cirrhosis and around 700 people get a liver transplant each year as a result of the condition (British Liver Trust). People with cirrhosis may show no symptoms or signs of liver disease for many years and so do not come to the attention of health services until their disease progresses and they develop major complications such as jaundice or fluid retention which can manifest as swelling of the abdomen or lower limbs, bleeding from their upper gastrointestinal tract or changes in their mental status.

1.3 Diagnostic and care pathway

Currently, transient elastography (FibroScan) is predominantly used in secondary care. The NICE guideline on Cirrhosis in over 16s recommends that transient elastography is offered for initial assessment to diagnose cirrhosis for:

- people with hepatitis C virus infection
- men who drink over 50 units of alcohol per week and women who drink over 35 units of alcohol per week and have done so for several months
- people diagnosed with alcohol-related liver disease.

The guideline further states "Offer either transient elastography or acoustic radiation force impulse imaging (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 enhanced liver fibrosis [ELF] test)." It is not recommended to offer tests to diagnose cirrhosis for people who are obese (BMI of 30 kg/m^2 or higher) or have type 2 diabetes unless they have NAFLD and advanced liver fibrosis (as diagnosed by a score of 10.51 or above using the ELF test). People diagnosed with cirrhosis on transient elastography are

referred to a specialist in hepatology. Retesting for cirrhosis is recommended to be offered every 2 years for:

- people diagnosed with alcohol-related liver disease
- people with hepatitis C virus infection who have not shown a sustained virological response to antiviral therapy
- people with NAFLD and advanced liver fibrosis.

The NICE guideline on Hepatitis B (chronic) recommends transient elastography as an initial test for liver disease in adults newly referred for assessment and for the annual reassessment of liver disease in adults who are not taking antiviral treatment. It is recommended that liver biopsy is considered to confirm the level of fibrosis in adults with a transient elastography score between 6 and 10 kPa. Liver biopsy is also recommended for adults with a transient elastography score less than 6 kPa if they are younger than 30 years and have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females) on 2 consecutive tests conducted 3 months apart.

The NICE guideline on non-alcoholic fatty liver disease states that use of the enhanced liver fibrosis (ELF) test should be considered in people who have been diagnosed with NAFLD to test for advanced liver fibrosis. However, if this test is not available, FibroScan is used here in current practice. FibroScan is included as a suggested test for use in the context of fibrosis assessment done for people with NAFLD in an algorithm proposed by the British Society of Gastroenterology.

Treatment

NICE's guideline on the assessment and management of non-alcoholic fatty liver disease recommends 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. People with NAFLD who drink

alcohol are also advised of the importance of staying within the national recommended limits for alcohol consumption.

The guideline makes the following recommendations on pharmacological treatment for people with advanced liver fibrosis:

- 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.

There is no cure for liver cirrhosis. Medicines offered to people with liver cirrhosis depend on the cause of liver damage. NICE's Clinical Knowledge Summary on Cirrhosis highlights that primary care management of cirrhosis includes offering advice on healthy eating, diet and alcohol consumption, medication review, being alert to features of potential complications of cirrhosis and referral to appropriate hepatology specialists. NICE guideline on Cirrhosis in over 16s: assessment and management includes recommendations on monitoring and managing complications of cirrhosis.

1.4 Regulatory status

FibroScan is a CE marked medical device (class IIa).

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Enables earlier or more accurate diagnosis
- Reduces risks, side effects or complications
- Enables a test, procedure or treatment to be done non-invasively
- Enables behaviour changes or lifestyle interventions

The benefits to the healthcare system claimed by the company are:

- Enables delivery of care in primary care setting (e.g. GP or community services) rather than in secondary care setting.
- Increases compliance
- Requires less time
- Reduce unnecessary referrals to secondary care

Some of the benefits of FibroScan claimed by the company may capture benefits that would only be realised from wider, or earlier, use of the technology. However, this guidance will only consider FibroScan as currently used in the NHS (that is, not in a wider population or extent of use) but used in primary care, rather than secondary or specialist care.

2 Decision problem

Population	People having a FibroScan to assess for liver fibrosis or cirrhosis (as per current NHS practice)
Intervention	FibroScan done outside secondary or specialist care (for example, GP or community services).
Comparator	FibroScan done in secondary or specialist care
Outcomes	The outcome measures to consider include: • Test accuracy • Agreement between measurement made by FibroScan done in primary and secondary/tertiary care

	• Comparative performance between different FibroScan models • Test failure • Uptake of offered FibroScan test • Uptake of behavior/ lifestyle change intervention • Number of referrals to secondary care • Number of people referred to alcohol or weight management services • Severity of liver fibrosis • Device-related adverse events • Use of NHS services (for example, GP or outpatient appointments) • Mortality • Morbidity (such as liver cirrhosis, liver related complications, cardiovascular complications)
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	Use of Fibroscan in specific populations, for example for people with: • Non-alcoholic fatty liver disease • Suspected non-alcoholic fatty liver disease (for example, people with metabolic syndrome or type-2 diabetes) • Alcohol-related liver disease • Suspected alcohol-related liver disease (for example, based on hazardous alcohol use) • Hepatitis
Special considerations, including those related to equality	Fibroscan may have higher failure rates in people with higher BMI, particularly for people with central obesity, where possible data reporting failure rates in this group should be extracted. People from Black African, African Caribbean and South Asian (Indian, Pakistani, Bangladeshi) backgrounds are at a higher risk of developing type 2 diabetes from a younger age and therefore have a higher risk of liver disease. People with alcohol or substance misuse are at higher risk of liver disease. Liver cirrhosis may in the long term, prevent a person from performing their normal day-to-day activities. Disability is a protected characteristic under the Equality Act 2010.

Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable	

3 Related NICE guidance

Published

Non-alcoholic fatty liver disease (NAFLD): assessment and management (2016) NICE guideline (NG49)

Cirrhosis in over 16s: assessment and management (2016) NICE guideline (NG50)

Hepatitis B (chronic): diagnosis and management (Published 2013, updated 2017) NICE Clinical guideline (CG165)

4 External organisations

The following organisations have been invited to register as stakeholders.

4.1 Professional

- British Society of Paediatric Gastroenterology, Hepatology and Nutrition
- Faculty of Public Health
- Royal College of General Practitioners
- Royal College of Physicians
- Royal College of Nursing

- British Society of Gastroenterology
- Royal Society of Medicine
- Royal College of Radiologists
- Royal College of Pathologists
- The Association of Clinical Pathologists
- British Association for the Study Of The Liver
- British Liver Nurses' Association
- British Liver Transplant Group
- The British Viral Hepatitis Group
- Royal Society for Public health UK
- Society for Endocrinology

4.2 Patient

- Black Health Agency
- Equalities National Council
- Muslim Council of Britain
- South Asian Health Foundation
- Liver4Life
- Children's Liver Disease Foundation
- British Liver Trust
- The Hepatitis C Trust
- Guts UK

NICE National Institute for Health and Care Excellence

Adoption report: FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care

Summary

Adoption levers identified by contributors

- Portable machines may be moved between sites and rooms.
- Care may be delivered closer to home.
- Non-invasive.
- May lead to an earlier diagnosis and may prevent progression to cirrhosis.
- Instant result that can be fed back to the patient immediately.

Adoption barriers identified by contributors

- Other tests may still be required to diagnose fibrosis and cirrhosis.
- Identifying a budget to purchase the technology and resources.
- May move secondary care pressures to primary care.
- Maintenance of FibroScan.
- Initial training and maintaining user competency.
- Developing and implementing a new pathway to diagnose and manage patients in primary care.

1 Introduction

The adoption team has collated information from 10 healthcare professionals working within 9 NHS organisations, 5 of whom have experience of using FibroScan. It has been developed for the diagnostic advisory committee (DAC) to provide context from current practice and an insight into the potential levers and barriers to adoption. It does not represent the opinion of NICE or DAC.

This adoption report includes some of the adoption considerations for the routine NHS use of the technology.

FibroScan has been available in the UK since 2005. It is currently used in 338 organisations in the UK: 300 in secondary care,15 in primary care, and the remaining in prisons, research units and drug misuse rehabilitation units.

The following FibroScan machines are available. Three machines are battery powered and 2 of these machines are fully transportable due to their small size, low weight and may be available from January 2022.

	Portable system	**Battery powered**	**Weight (kg)**
FibroScan 230 / FibroScan Go (The company states that FibroScan 230 will be launched in the UK in 2022)	Mobile	No	4.4
FibroScan 430 Mini and M probe (The company states that FibroScan 430 mini will not be sold from January 2022)	Mobile	Yes	5
FibroScan 430 Mini+ and M probe	Mobile	Yes	5
FibroScan 530 Compact and M probe	Transportable	Yes	10
FibroScan 630 Expert Spleen Pack and M probe	No	No	46

FibroScan is sold with the following 3 different size probes:

- small (S): recommend for paediatric use
- medium (M)
- extra-large (XL): recommended for use with obese people.

The company state 96% of FibroScan machines are sold with a M and XL probe. FibroScan machines and the probes work for up to 7 years. There are 2 packages available for the 2 fully transportable machines, as follows:

Capital purchase	Pay per scan (FS 'Go' package)
This package includes initial purchase of components which may include 430 Mini+ or 530 Compact with M probe, XL probe, Smart Exam, training for up to 3 people, installation. Following a 12-month warranty period service packages are offered depending on the machine model or there is an option of a calibration only service.	This package includes payment on a pay per patient scan completed (consists of 10 valid measurements). Minimum 25 scans per month invoiced. Actual scan volume invoiced over 25 scans. Includes hardware, 2 probes (M and XL), training, installation, service, calibration costs, 36-month minimum contract term with an option to renew 12 monthly thereafter. No upfront capital cost and no transfer of ownership. User supplies computer with internet connection to upload and share results if required.

2 Contributors

Details of contributing individuals are listed in the below table.

Site	Job title	Setting	Experience
1	GP and senior clinical lecturer	Primary care	Non-user
2	GP and senior clinical lecturer	Primary care	Non-user
3	GP and clinical director in a CCG	Primary care	Non-user
4	Commissioning manager	CCG	Non-user
5	Senior commissioning manager	CCG	Has 1 machine since 2017 in primary care. Pilot started as an outreach service from secondary care. Now provided by community tier 2 service funded using a locally agreed tariff by secondary care. Used with 667 people in past 18 months.
6	Consultant hepatologist Service coordinator for liver and alcohol service	Secondary care	Have 5 machines since 2014 in secondary care. Was providing an outreach service to primary care prior to COVID-19. Used 5 days a week

7	Consultant hepatologist and gastroenterologist	Secondary care	Has 2 machine since 2014 in secondary care. Carries out 1500-2000 scans per year. Was providing an outreach service to primary care prior to COVID-19. Used 2 days a week.
8	Consultant gastrointestinal pathologist	Secondary care	Non-user
9	Consultant hepatologist	Secondary care	Have 4 machines since 2014 in secondary care, were providing an outreach service to primary care prior to COVID-19. Used 7 days a week.

3 Current practice in clinical area

The following tests may be used in primary care to diagnose or investigate liver fibrosis and cirrhosis. The types used depends on local commissioning arrangements and access to tests.

- enhanced Liver fibrosis (ELF) blood test
- fibrosis-4 (FIB-4) test
- fibroTest-ActiTest blood test
- intelligent liver function testing (iLFT) test
- lifestyle questions, for example about drug use and alcohol consumption
- liver function tests (LFT)
- NAFLD Fibrosis test
- physical examination
- ultrasound scan

Following the outcome of these tests, the GP may categorise the person as follows.

- high risk: refer to secondary care
- borderline to low risk: managed in primary care

In secondary care, the following tests may be used to investigate liver fibrosis and cirrhosis (further to the tests used in primary care):

- Transient elastography such as a FibroScan (waiting time from GP referral to scan is reported to be between 4 to 12 weeks).
- Referral to radiography for further imaging, such as MRI, CT scan, Magnetic Resistance Elastography (MRE) or 2D shear wave ultrasound and elastography.
- Liver biopsy may be used when results of previous tests are inconclusive and for high priority cases. Prior to a liver biopsy, an INR, platelet count and full blood count may be required to determine the person's risk of post-biopsy bleeding. There are 2 types of liver biopsy commonly available: a percutaneous biopsy and a trans-jugular biopsy. The risk of post-biopsy bleeding would determine the type of biopsy required. Liver biopsy is usually a day case procedure but may rarely include an overnight stay.

4 Use of FibroScan in practice

The person must not eat or drink for 3 hours before the scan. A probe is placed on the abdomen with the person lying down. The scan is repeated 10 times for an accurate result. An algorithm analyses the returned wave to determine its speed in meters per sec (m/s) and the equivalent stiffness in kilopascals (kPa).

Users report that FibroScan may sometimes be unsuccessful and not provide accurate results. Suggested reasons for this are a high BMI, ascites, recent food consumption or inexperience of the person performing the scan. Unsuccessful scans vary between contributing sites from less than 1% to 20%.

Management of unsuccessful scans depends on the urgency of the case. Users may offer a FibroScan on another day, refer to radiography for further imaging or refer for a biopsy.

Results are either interpreted at the time or sent back to the referrer. Some users offer a scan only appointment of 15 to 20 minutes. Others offer a scan and consultation taking 30 to 40 minutes. When interpreting the results, other test results will also be considered before a diagnosis is made. All users stated they will not diagnose using a FibroScan result alone.

5 Reported benefits

The potential benefits of adopting FibroScan, as reported to the adoption team by the healthcare professionals using the technology are:

- Portable machines may be moved between sites and rooms.
- Care may be delivered closer to home.
- Non-invasive.
- May lead to an earlier diagnosis and may prevent progression to cirrhosis.
- Instant result that can be fed back to the patient straight away.

6 Insights from the NHS

Area of application in the NHS and care pathway

Contributors agree a separate appointment for FibroScan would be required after an initial GP consultation and after primary care tests have been carried out. Primary care contributors are concerned about the time and cost pressures of developing and implementing new care pathways to diagnose and manage patients currently referred to secondary care.

None of the primary care contributors have experience of using FibroScan and all said they did not have confidence that it would add anything significant to the primary care tests currently used in managing low-risk patients in primary care. One was concerned that using FibroScan would result in over screening in primary care. All agreed there may be an unmanageable shift of patient numbers from secondary care to primary care. They expressed concerns that a large volume of people would need scanning to maintain cost effectiveness and staff competency. One suggested an outreach service from secondary care, may help address some of these concerns. A

secondary care contributor who provide an outreach service to primary care agreed an outreach service is the only model that would work at their primary care setting. Two stated they would prefer an ultrasound machine over FibroScan because it can be used across a range of different conditions.

Patient selection

Contributors agree alcohol misuse and obesity are a growing public health concern. These public health issues, together with other factors such as type 2 diabetes can increase a person's risk of developing fibrosis and cirrhosis. Some people with cirrhosis and fibrosis are incidentally diagnosed in A&E or in primary care when they are being investigated for a related condition. There was agreement that FibroScan may help earlier diagnosis leading to a reversal of liver damage and prevention of disease progression.

Resource impact

Identifying a budget for FibroScan is stated to be an adoption barrier by all primary care non-users. Contributors added significant funding would be required to fund the technology, pathway, accommodation, and staffing. The CCG contributor have a 'pay per scan' contract with the company.

Training

The company provide half a day essential onsite training which includes a 1-hour lecture, followed by a practical session on 3 case studies. Upon successful completion, the user is certified by the company. Virtual training is also offered when onsite visits are not allowed. Some users have been required to fulfil local training following that provided by the company. This has included supervision during scans and training on the local pathway and interpreting results.

Not all FibroScan users have a medical background and include band 3 to band 4 health care assistants, band 5 to 7 nurses and research fellows.

Users report that, irrespective of qualifications, experienced scanners get less unequivocal results. It is therefore good to maintain competency by regular use of the technology.

Patient experience

Contributors agree people at risk of fibrosis and cirrhosis may benefit from an earlier diagnosis before they develop irreversible liver damage. They may be more likely to attend local appointments in primary care rather than secondary care. Therefore, it may be beneficial to offer FibroScan in primary care. Primary care non-users, however, stated that moving appointments and management to primary care may be beneficial for many people currently managed by secondary care services but would put primary care under a lot of pressure.

Most contributors agree that people would prefer a FibroScan over a liver biopsy if given the option in high priority cases because it is a quick and painless scan that can give immediate results. It is not reported to have any potential complications or risks and is non-invasive.

Maintenance

Some users have a maintenance contract where the machine and probe are serviced and calibrated annually by the company. The company may loan an alternative machine during service and calibration.

At one site, FibroScan was used in error when calibration of the machine had expired 3 months previously. The trust had to recall and rescan all the patients and assure calibration is now arranged with the company by a dedicated member of staff.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT562 FibroScan for assessing liver fibrosis and cirrhosis in primary care

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	Echosens
Submission date	21 September 2021
Regulatory documents attached	CE certificate Clinical Evaluation Report Instructions for Use
Contains confidential information	No

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People having a Fibroscan to assess for liver fibrosis or cirrhosis (as per current NHS practice)	Enter text.	Enter text.
Intervention	FibroScan done outside secondary or specialist care (for example, GP or community services).	Enter text.	Enter text.
Comparator(s)	FibroScan done in secondary care or specialist care	Enter text.	Enter text.
Outcomes	The outcome measures to consider include: • Test accuracy • Agreement between measurement made by FibroScan done in primary and secondary/tertiary care • Comparative performance between different Fibroscan models • Test failure • Uptake of offered Fibroscan test • Uptake of behavior/ lifestyle change intervention • Number of referrals to secondary care • Number of people referred to alcohol or weight management services • Severity of liver fibrosis • Device-related adverse events	Enter text.	Enter text.

	• Use of NHS services (for example, GP or outpatient appointments) • Mortality • Morbidity (such as liver cirrhosis, liver related complications, cardiovascular complications)		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	Enter text.	Enter text.
Subgroups to be considered	Use of FibroScan in specific populations, for example for people with: - Non-alcoholic fatty liver disease - Suspected non-alcoholic fatty liver disease (for example, people with metabolic syndrome or	Enter text.	Enter text.

	type-2 diabetes) - Alcohol-related liver disease - Suspected alcohol-related liver disease (for example, based on hazardous alcohol use) - Hepatitis		
Special considerations, including issues related to equality	Fibroscan may have higher failure rates in people with high BMI (40 or greater). People from Black African, African Caribbean and South Asian (Indian, Pakistani, Bangladeshi) backgrounds are at a higher risk of developing type 2 diabetes from a younger age and therefore have a higher risk of liver disease. Liver cirrhosis may in the long term, prevent a person from performing their normal day-to-day activities. Disability is a protected characteristic under the Equality Act 2010.	Enter text.	Enter text.

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	FibroScan® 630 Expert FibroScan® 530 Compact FibroScan® 430 Mini+ FibroScan® 230 Go
Approved name	FibroScan®
UKCA/ CE mark class and date of authorisation	Class IIa according to Rule 10 of Appendix IX of Directive 93/42/EEC

Version(s)	**Launched**	**Features**
FibroScan® 530 Compact	Since 2016	Liver stiffness and SmartExam as an option
FibroScan® 430 Mini+	Since 2016	Liver stiffness and SmartExam as an option
FibroScan® 630 Expert	Since 2019	Liver stiffness, spleen stiffness and SmartExam as an option
FibroScan® 230 Go	Since 2021	Liver stiffness and SmartExam as an option

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Enables earlier or more accurate diagnosis	Systematic literature review De novo cost model to be submitted in Part 2	Implementing FibroScan in primary care instead of secondary care enables earlier diagnosis of chronic liver diseases which are silent diseases. This will avoid to diagnose late stage fibrosis or cirrhosis in secondary care. The different studies presented a valid measure rate from 91% to 98%.
Enables a test, procedure or treatment to be done non-invasively	Systematic literature review (1) and all the cohort studies	So far, the gold standard to diagnose liver fibrosis and cirrhosis was liver biopsy. Liver biopsy was performed in secondary care and mostly for late stages patients. Liver biopsy is performed in a secondary setting with mortality and morbidity risks for the patients.
Reduces risks, side effects or complications	Absence of adverse events in the clinical evidence	FibroScan examination is a non-invasive procedure with no adverse events reported in any international databases.
Enable behaviour changes or lifestyle interventions	Systematic literature review (1) and all the cohort studies De novo cost model to be submitted in Part 2	Lifestyle modification is an effective therapy to downgrade hepatic injury

System benefits		
Enables delivery of care in primary care setting (e.g. GP or community services) rather than in secondary care setting	Systematic literature review (1) and all the cohort studies De novo cost model to be submitted in Part 2	
Increase compliance	Cohort studies like Mansour et al (2,3)	Patients were more likely to attend a FibroScan examination when proposed in primary care. The rate of missed appointments are lower in primary care. This affects the patients' uptake of the technology.
Avoid unnecessary referrals to secondary care	Cohort studies like Rhodes et al (4) De novo cost model to be submitted in Part 2	Each of the successful local schemes for earlier diagnosis have led to a reduction in unnecessary referrals to hospital based consultant clinics with consequent cost savings.
Requires less time	De novo cost model to be submitted in Part 2	By avoiding unnecessary referrals, the patient pathway saves time for both patients and healthcare professionals. The patient does not have to book an appointment at a NHS Hospital Trust or liver clinic to have a FibroScan examination. From a healthcare professional perspective, FibroScan examination can be done by any trained operator so It does not requires

		physician or a high band nurse time.
Cost benefits		
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Sustainability benefits		
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

The FibroScan main unit comprises an external or internal power supply (depending on the model), a dedicated electronic (elastography engine) and a personal computer. It also serves as support for probe holders. The main unit is either a cart or a portable device (depending on the model). The FibroScan is controlled by a custom software application that is automatically launched on power up.

The FibroScan operates with an ultrasound probe, the same used for the already CE-marked FibroScan devices.
The FibroScan probe comprises a single-element ultrasound transducer mounted on the shaft of the electrodynamic transducer.

Three models of probes may be used depending on patient morphology: **S probe, M probe, XL probe**. Each of the probes embeds a different ultrasound transducer. The probe ultrasound transducer is the only part of the FibroScan that enters into contact with the patient.

The technology used by FibroScan devices, i.e. the Vibration-Controlled Transient Elastography (VCTE) technology.

Vibration-Controlled Transient Elastography (VCTE)

All FibroScan models operates based on the Vibration-Controlled Transient Elastography (VCTE) method. The FibroScan probe comprises a single-element ultrasound transducer mounted on the shaft of an electrodynamic actuator. This transducer generates a transient vibration, which in turn generates an elastic shear wave at a controlled 50 Hz center frequency. This wave propagates through the skin, the subcutaneous tissues, and then the liver. During the shear wave propagation, the ultrasound transducer contained in the tip performs a series of ultrasound acquisitions (emission/reception) to measure the speed of shear wave propagation, also named shear wave speed or SWS, in the liver. Shear wave speed in m/s and associated **liver stiffness measurement** (LSM) in kPa are calculated using the standard VCTE algorithm. Values range between 1.5 and 75.0 kPa.

Controlled Attenuation Parameter - optional

The CAP (Controlled Attenuation Parameter) in dB/m is a measure of the attenuation of ultrasonic signals in the tissue at a frequency of 3.5 MHz regardless of the FibroScan probe being used. **CAP™ is optional** when using the FibroScan devices for both former and new generations of the device.

Launched in 2021, SmartExam is a new computation method allows continuous measurement of CAP™ during the entire examination. In addition, when CAP™ measurement does not meet the quality criteria they are automatically rejected. This allows a deeper assessment of liver fibrosis and steatosis

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

FibroScan devices are reusable devices (this is also applicable to the former generations of the devices).

All FibroScan devices are manufactured in France and then shipped to the UK.

FibroScan 530 Compact, 430 Mini+ and 230 Go are wearables and can be move from one facility to another with the appropriate brief case in order to reduce the travel distances for patients.

Echosens guarantees the specifications and performance characteristics of the FibroScan device for seven years, provided that all necessary precautions for use and maintenance have been taken in accordance with the recommendations of the user manuals provided. The FibroScan uses a 'button cell' battery. This is a long-life battery and it may never need replacing.

FibroScan does not have consumables (except the water-based jelly), does not need medical gases or full disinfection (except the probe transducer) after each utilisation.

One the claims benefit of FibroScan outside secondary care and specialist care is to avoid unnecessary referrals.

FibroScan may reduce the number of visits to hospital that the patient is required to make to undergo an examination because the FibroScan is readily available and easily fitted at the primary care facility. As a result, patients travel fewer miles and the environmental impact of transport is decreased.

The FibroScan systems are not likely to increase the quantity of electricity, fuels, water and types of waste generated from the GP consultation for the specific condition

3 Clinical context

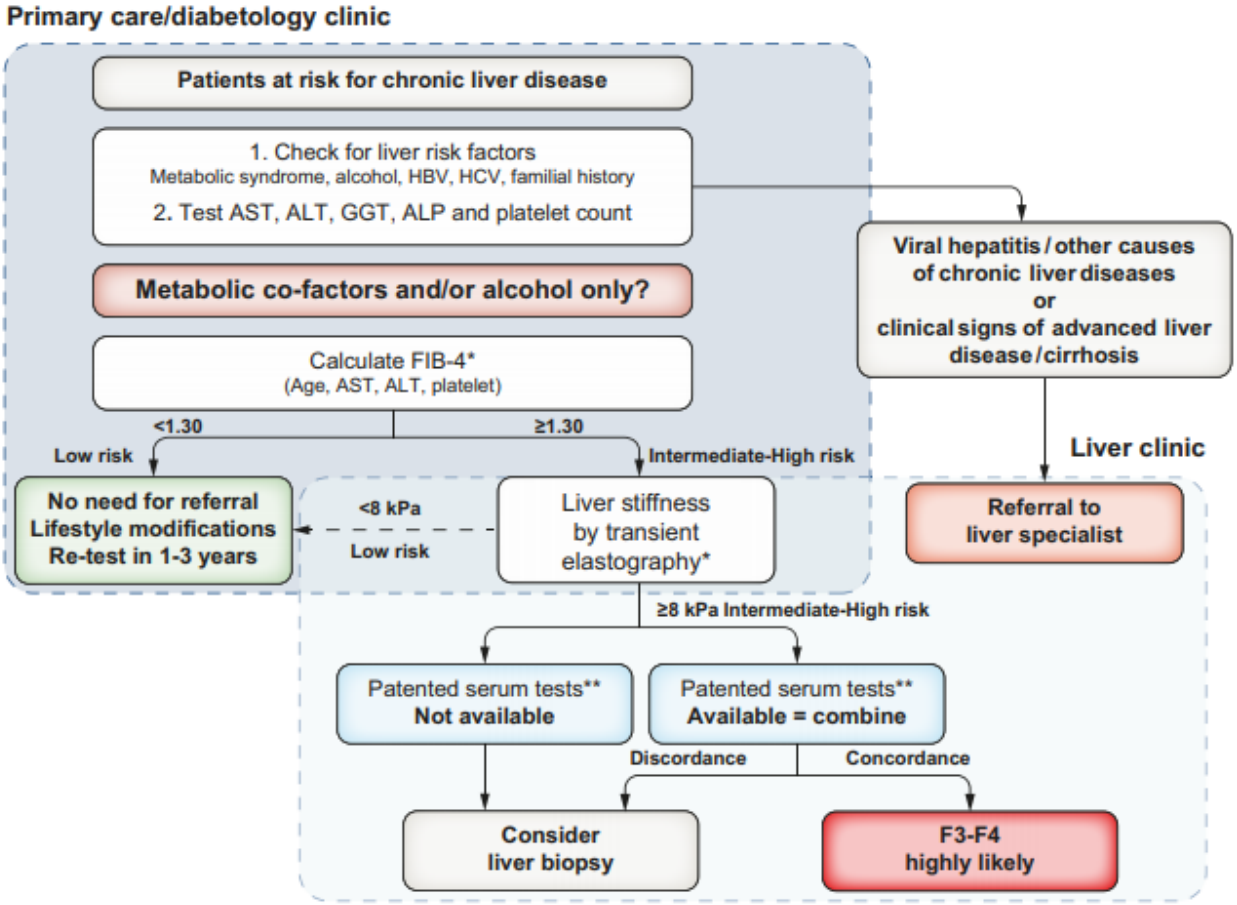
Currently, transient elastography (FibroScan) is predominantly used in secondary care for the diagnosis and management of patients with chronic liver disease. Transient elastography is recommended in the patient pathway in several guidelines:

- NICE guideline on Cirrhosis in over 16s,
- NICE guideline on Hepatitis B (chronic)
- NICE guideline on non-alcoholic fatty liver disease

However, this guidance will only consider FibroScan as currently used in the NHS (that is, not in a wider population or extent of use) but used in primary care, rather than secondary or specialist care.

There is no official pathway informed in any NICE Guidance related to assessing liver fibrosis and cirrhosis outside secondary care and specialist care.

We propose the following patient pathway with FibroScan (transient elastography) performed outside secondary or specialist care setting level as a reference.



The clinical care pathway presented above comes from the last European Association for the Study of the Liver (5), Clinical practice guidelines on non-invasive tests for evaluation of liver diseases severity and prognosis. This figure is a proposed use of non-invasive tests in patients observed in primary care or outside the liver clinic. As shown, a 2-step strategy including a non-invasive free blood test such as FIB-4 can be used in patients with metabolic co-factors such as Type 2 diabetes, metabolic syndrome and obesity and/or hazardous alcohol use to identify patients requiring referral to the specialist liver clinic. Transient elastography (FibroScan) and FIB-4 can be performed before referral to liver specialist according to local availability and pathways.

However, there are multiple liver pathways across the UK to assess liver fibrosis, each CCG having the possibility to come with its own pathway, depending on the

aetiologies of the liver disease (viral hepatitis, at-risk NAFLD/NASH patients and harmful alcohol use).

The British Liver Trust mapped the results of a survey regarding CCGs primary care pathway status for liver disease.

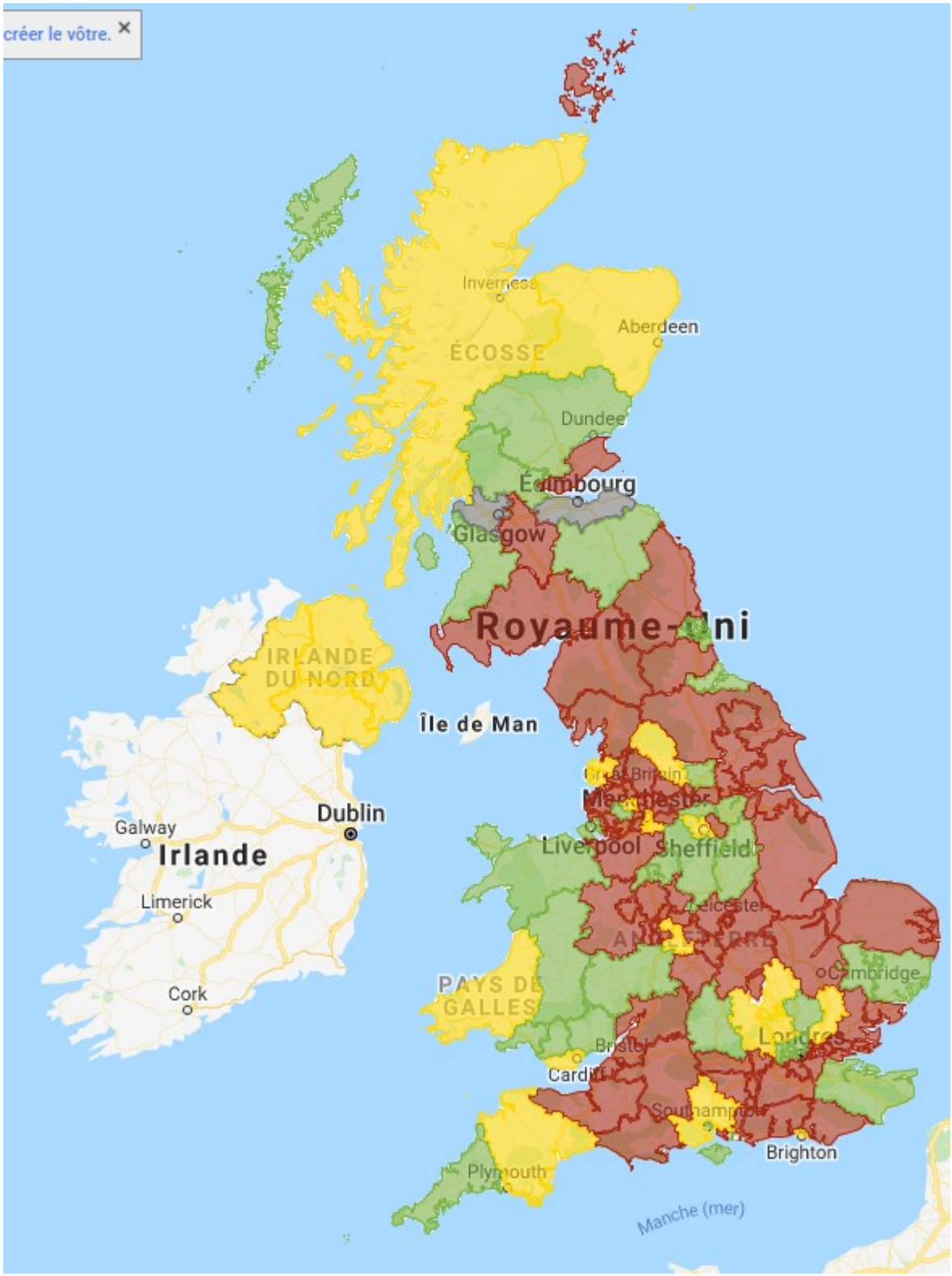


Figure 1: Liver pathway map per CCG

The map shows four different colours, each corresponding to a different status:

- Red: No commissioned liver pathway
- Amber: Partial liver pathway or liver pathway in development
- Green: Full liver pathway in place
- Black: Did not respond

The map and data are available here: Improving early diagnosis of liver disease - British Liver Trust

The detection of early liver disease by screening in primary and community care was highlighted by the Nottingham pathway (called “The Scarred Liver Project”). The pathway has evolved to allow general practitioners and patient’s greater access to transient elastography based on risk factors alone (T2DM, obesity, alcohol excess, etc.). (6)

The pathway has been adapted for trials in other areas included within community drug and alcohol services in Chesterfield and within a regional primary care super-practice (that serves a population of 200 000 people). The forward focus is on developing the brief lifestyle advice provided to all patients into a more supportive and sustainable behaviour change intervention. (6)

Inclusion of the early detection programme in an updated NHS Health Check, in line with NICE guideline Cirrhosis over 16s will add substantially to the value of these health checks.

The figure below presents the results of the Hepatology-based referrals versus community-based referrals in Southampton and Nottingham Primary Liver Care Pathway from 2015 to 2019.

Each of the successful local schemes for earlier diagnosis have led to a reduction in unnecessary referrals to hospital based consultant clinics with consequent cost savings. Showing the effects on survival and state of health will require larger cohorts and longer periods of follow-up.(6)

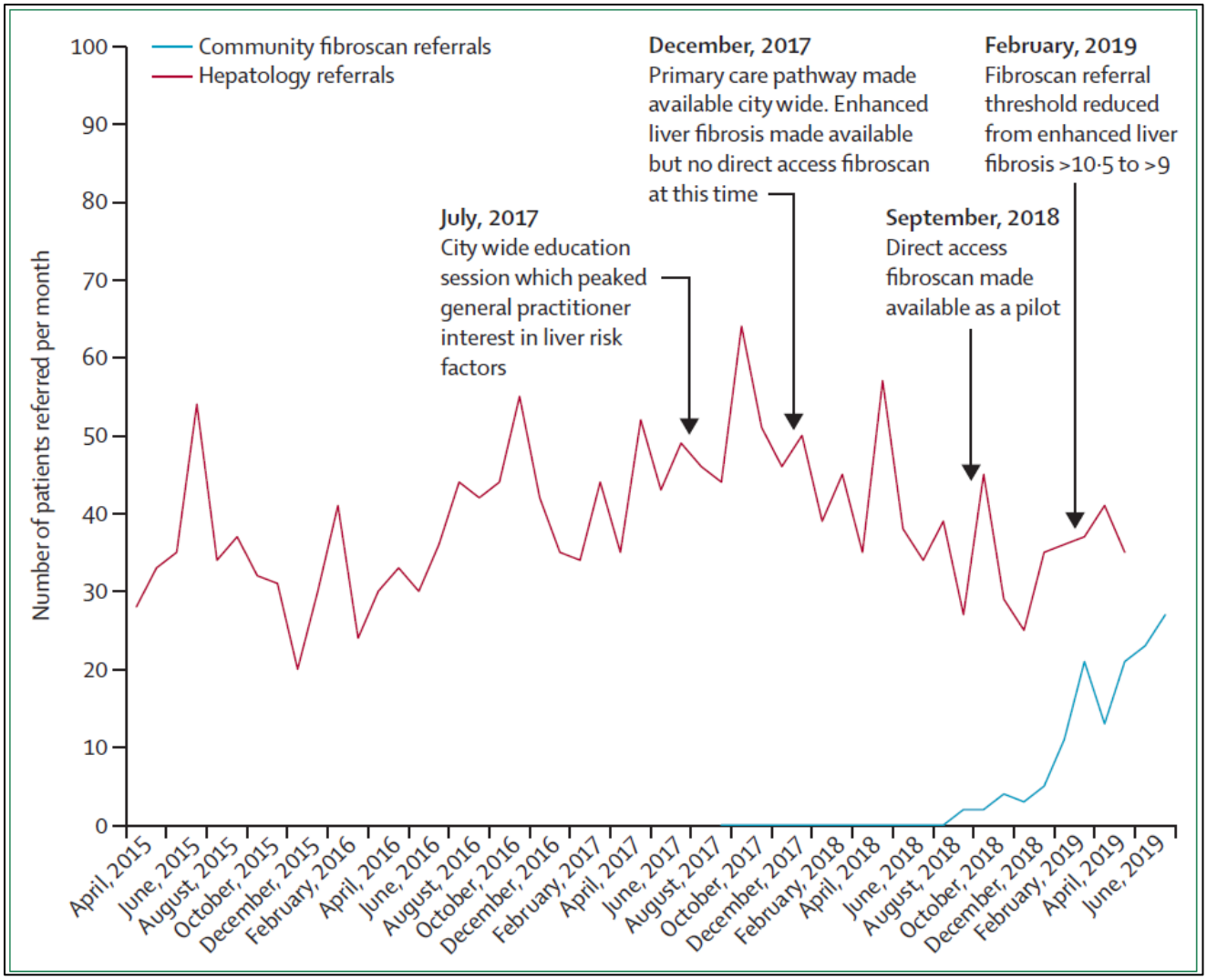


Figure 2: Hepatology-based referrals versus community-based referrals in Southampton Primary Liver Care

Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

The training should be provided to any clinical staff (physician, nurse, clinical research associate, etc.) in charge of operating one or several types of FibroScan systems. The training has to be done on site where the system is installed and by a member of the Echosens team.

The training includes 2 parts:

- Theory for 60-75 min
- Practice (liver examination) for 120 minutes to 180 minutes depending on the number of participants

During practice, participants will have to use the FibroScan system and to perform real examinations on liver depending on the FibroScan model. Every trainee will have to perform at least 3 full examinations on 3 different volunteers (patients or members of local facility staff).

Altogether, the training session takes half a day for a maximum of 3 participants. Each participants will then receive a training certificate from Echosens stating they can use FibroScan as trained operators.

Training will typically cover the following items:

Before the examination

- Installation/position of patient
- Position of the operator
- Anatomical marks to find liver location
- Holding the probe

Making a reliable measurement

- Interpreting Ultrasound signals (TM, A mode) images and choose an appropriate measurement spot, control of the Liver Targeting Tool indicator (green bar).
- Perpendicular position of the probe
- Identifying a good or defective measurement by checking shear wave maps/elastograms
- (illustrated support provided, “Reminder Sheet”)
- Identify probe recommendation tool on the screen (“M probe advice, or XL probe advice”)
- Identify Elasticity and CAP* results displayed on screen (*where applicable, not FS 430 Mini)
- Explanation of displayed values for Elasticity and CAP* (median, current value, IQR,
- IQR/Median ratio in %)
- Quality criteria : At least 10 valid measurements at the same spot, IQR/Median
- recommendation for elasticity
- Erasing measurements

- Intentional failures (measurement on a rib, measurement made without gel, presence of veins, probe non perpendicular, measurement performed in the border of the liver)

FibroScan Software interface

Archive mode

- Delete an examination
- Delete a patient file
- Advanced search function
- Viewing an examination from the “Archives” database
- Export function on USB support (PDF Report, MS Excel spreadsheet, FIBX files)

Acquisition screen

- Entering patient’s data
- Work list function
- Automatic probe selection tool
- Liver Targeting Tool indicator
- Adding comments during the exam
- Change of probe within the exam
- Export examination (PDF, FIBX file)
- Print button
- Hide patient data function
- Detailed exam conditions at the end of exam

Safety instructions

- Disinfecting and cleaning the probe
- Use non-alcoholic solution for disinfection
- Follow the probe recommendation criteria.
- Non-waterproof warning
- Replacing the probe on its support
- Warning regarding fasting conditions

There is no training needed for the patient.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		53
Number of studies identified as being relevant to the decision problem.		7
Of the relevant studies identified:	Number of published studies (included in table 1).	7
	Number of abstracts (included in table 2).	0
	Number of ongoing studies (included in table 3).	0

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
PubMed	Mansour, 2021, UK (2)	Real-world study	Patients > 35 years with T2DM attending annual review at two primary care practices. There were no lost to follow up. 7% of patients did not attend their appointments for TE. Of the remaining 24 patients who were not referred for FibroScan, 20 were considered unsuitable for further investigation by the referring GP because of frailty/life limiting illness (17), inability to give consent (1), or were already known to gastro/ hepatology services (2), and 4 patients died during the pilot period	The non-invasive tests used were the following ones: • Liver Function tests (LFTs) • FIB-4 • Transient Elastography	Not applicable as the study is not a comparative study	Primary outcome of this real-world study was the number of patients with advanced fibrosis/cirrhosis identified through the pathway. Secondary outcomes were service uptake (number of patients declining or not attending tests), and predictors of advanced fibrosis.
PubMed	Harman, 2015, UK (7)	Prospective cross-sectional study	The total patient population of the two participating general medical practices was 12 368, of which 10 479 patients were adults. In total, 5922 adult patients (56.5%) had alcohol consumption documented, with 6.3% of the total GP population (658 patients) meeting our definition for hazardous alcohol use. The adult prevalence of type 2 diabetes was 3.7% (390 patients). Both of these risk factors were found in 21 patients and thus 1027 patients were identified for the study. We excluded 107 patients and therefore 920 were invited to the study	Overall, 504 patients (54.8%) underwent the simple blood- based biomarker. In total, 378 patients underwent TE, of whom portable M-probe readings were performed in 361 patients.	Not applicable as the study is not a comparative study	Diagnosis of clinically significant liver disease (defined as liver stiffness ≥8 kPa); definitive diagnosis of liver cirrhosis.

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			Of the excluded patients eight had prior definitive staging of liver disease due to alcohol (3 patients), hepatitis B (2), non-alcoholic steatohepatitis (NASH; 1), haemochromatosis (1) and primary biliary cirrhosis (1).			
PubMed	Harris, 2017, UK (1)	Systematic review	Studies were included if the study was done in adults aged 18 years or older; the study population was from a non-hospital setting (eg, community, primary care, or outreach unit); the study participants underwent a validated non-invasive test, which would stratify for liver fibrosis; the prevalence of clinically significant liver disease, either liver fibrosis or cirrhosis, was reported as an outcome measure by the study and the study participants were recruited from an unselected population or on the basis of the participants' age, or a defined risk factor for alcoholic liver disease or non-alcoholic fatty liver disease. Studies were excluded if the data regarding the study population, the setting in which the non-invasive test was completed, or the threshold for the non-invasive test were not adequately reported; the participants were solely investigated for liver disease causes other than alcoholic liver disease or	The non-invasive test used are the following ones: • Transient elastography • AST to ALT ratio • APRI score • BARD score • FIB-4 score • NAFLD fibrosis score • FibroTest • Hyaluronic Acid • BAAT score • Southampton traffic light test	Not applicable as the study is not a comparative study	The primary aim of this systematic review was to assess the proportion of the studied populations found to have clinically significant liver disease as defined by the non-invasive tests used in the individual studies. The secondary aims were: to identify the proportion of patients with liver fibrosis or cirrhosis, as defined by the non-invasive test, who had normal ALT results; to assess the difference in the proportion of patients identified as

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			non-alcoholic fatty liver disease (e.g. viral hepatitis); or they were not published in English.			having liver disease with use of non-invasive tests between unselected or targeted populations within a community setting; and to determine the patient variables that are important in identifying patients with liver fibrosis. The outcome measure was the reported prevalence of liver fibrosis or cirrhosis, or both, within the population studied as defined by the non-invasive test that was used.
PubMed	Rhodes, 2020, UK (4)	Retrospective analysis	All general practitioner-referrals with suspected Alcoholic/non-alcoholic fatty liver disease (NAFLD) to a UK Hepatology-centre. A total of 2944 patients were referred to the hepatology service from primary care and of these, 762 (mean age 55.5±13.53 years) met the inclusion criteria for this study; 231 patients were	The non-invasive test used are the following ones: • Transient elastography • AST & ALT • APRI score • FIB-4 score • ELF test	Not applicable as the study is not a comparative study	Primary outcomes : Proportion of referrals with suspected ALD/NAFLD with advanced fibrosis as assessed by tertiary centre hepatologists using combinations of FibroScan,

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			referred with suspected ALD (mean age 54.68±12.37 years), and 531 with suspected NAFLD (mean age 55.88±14 years). One patient was deemed to have active hepatitis C virus infection as comorbidity and three were found to have inactive chronic hepatitis B after referral.			imaging, examination and blood tests and liver histology, where indicated. Secondary outcomes: Included impact of body mass index/alcohol consumption on the odds of a diagnosis of advanced fibrosis, and performance of NIT in predicting advanced fibrosis in planned post-hoc analysis of referrals.
PubMed	El-Gohary, 2018, UK (3)	Prospective, cluster randomised feasibility trial	A total of 7,183 patients were identified for further investigation: 715 were referred by a GP (Pathway 1), 4,397 participants were identified from a risk group (Pathway 2) and 2,071 responded to the AUDIT questionnaire (Pathway 3). In total, 2,082 patients were invited to liver clinic and 1,172 did not attend.	The non-invasive test used are the following ones: • Transient elastography • Blood-tests • STL (Southampton Traffic Light) test • ELF test • AUDIT questionnaire	10 GP practices were randomised to either intervention (liver health nurse) or control (care as usual). Pathway1: GP referral Pathway 2: Case-finding of risk factors Pathway 3: screening for excess alcohol	Post study practice audits of liver disease were carried out following the final recruitment of participants in the intervention practices, and also within the control practices.

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
PubMed	Harris et al, 2019, UK (8)	Prospective non comparative study	1023 patients were identified to have at least one of the risk factors (obesity, hazardous alcohol use and/or T2DM) on a total of 4,150 followed by the GP Practice. 576 patients attended the pathway	The non-invasive test used are the following ones : • Transient elastography	Not applicable as this is not a comparative study.	Effect of a raised body mass index on the risk of liver disease using data from a community risk stratification pathway.
PubMed	Harman et al, 2018 UK (9)	Cross-sectional study with recruitment	919 patients underwent transient elastography. The selected risk factors for inclusion were hazardous alcohol use and T2DM. All patients were recruited and measured within a primary care setting, amongst 4 different GP practices from the same area. 20 patients were without valid liver stiffness measurement	The non-invasive test used are the following ones : • Transient Elastography	Not applicable as this is not a comparative study	Screen at-risk individuals in general practice for undetected cirrhosis using transient elastography and study the risk factors underlying these cases.
Text	Text	Text	Text	Text	Text	Text

Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
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Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion) and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
Southampton CCG	Lucie Lleshi, Senior Commissioning Manager Karen Street, Head of Services. 2020 UK	Pilot prospective study	Patients were recruited within GP practices in the Southampton CCG. Patients are 18 years and over, registered with a Southampton City CCG GP and with a ELF test result ≥ 9 and/or alcohol consumption > 30 units/week.	The non-invasive test used are the following ones : • Transient Elastography • ELF test	Not relevant as this is not a comparative study	FibroScan examination attendance Referrals to Hepatology vs. discharged back to GP Hospital first outpatient activity.

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Mansour, 2021, UK (2)	A total of 85 /467 (18.5%) patients had raised Fib-4; 27/467(5.8%) were excluded as a result of frailty or known cirrhosis. A total of 58 /467 (12.2%) were referred for TE. Twenty-five of 58 (43.1%) had an LSM of >8 kPa and 13/58 (22.4%) had a LSM >15 kPa; 4/58 (6.7%) did not attend and 5/58 (9.3%) had an invalid reading. Twenty of 440 (4.5%) patients were found to have advanced liver disease following specialist review, compared to 3 patients previously identified through standard care (odds ratio [OR] 6.71 [2.0–22.7] p = 0.0022). Alcohol (OR 1.05 [1.02–1.08] p = 0.001) and BMI (OR 1.09 [1.01–1.17] p = 0.021) were predictors of	This study highlights the pathway linking primary and secondary care in the diagnosis and management of patients with chronic liver disease. This study targeted type 2 diabetes patient, which considered as at-risk patients for NAFLD/NASH. The authors used portable FibroScan 402, which is not sold anymore in the UK. However, there is consistency with all our FibroScan systems (current and past) as they assess liver stiffness by transient elastography with the same technique

	advanced disease, particularly drinking >14/21 units/week (p <0.0001)	Those results were also presented as a poster at the International Liver Congress 2021. More and more local teams with the support of NHS Trusts and CCG are implementing pathways incorporating a 2-tier assessment of liver fibrosis instead of current standard.
Harman, 2015, UK (7)	The authors identified 920 patients with the defined risk factors of whom 504 patients agreed to undergo investigation. A normal blood biomarker was found in 62 patients (12.3%) who required no further investigation. Subsequently, 378 patients agreed to undergo TE, of whom 98 (26.8% of valid scans) had elevated liver stiffness. Importantly, 71/98 (72.4%) patients with elevated liver stiffness had normal liver enzymes and would be missed by traditional investigation algorithms. The authors identified 11 new patients with definite cirrhosis, representing a 140% increase in the number of diagnosed cases in this population. Valid liver stiffness acquisition was possible in 366 patients (96.8%). A new diagnosis of clinically significant liver disease was made in 98 patients (26.8%) with valid TE measurement. This represents a substantial increase in diagnoses for these practices.	The identification of liver disease in the community, where previous studies have discovered a large burden of previously unidentified but significant liver disease, is therefore a feasible place to develop new liver disease investigation pathways using these non-invasive markers. The study ran from Feb 2012 to April 2013, quite some time ago. It included to 2 type of at-risk patients: Type 2 diabetics and patients with hazardous alcohol use. This study was conducted during the same period than Harman et al, 2015 (7), within the same community but on a lower number of GP practices. Some patients could be part of both studies. In collaboration with the Department of Health, Nottingham University Hospitals have commenced a pilot community liver disease pathway in two General Practices in Nottingham in February 2012. Patients with liver risk factors (hazardous alcohol use, obesity or type 2 diabetes) are invited to take part in the pathway. Patients undergo a simple blood test (AST:ALT ratio and BARD score), with a high test result requiring referral for a liver stiffness scan (Fibroscan) which is performed in the community setting. Preliminary findings show that the pathway accurately identifies patients with early liver scarring and previously unidentified significant liver disease. The participating General Practitioners have also noted a striking number of patients finally engaging in

		important lifestyle changes following pathway implementation. A second phase of the pilot pathway, in 2 Inner City General Practices with a total practice population of c.14,000 patients commenced in June 2013
Harris, 2017, UK (1)	The authors have shown in this systematic review that several non-invasive tests have the ability to stratify for the severity of liver disease within a community setting. Moreover, when compared with the uptake of other screening programmes, the participation of those invited suggests that as screening tests for the use in the community, non-invasive tests are more acceptable to patients. The prevalence estimates of cirrhosis (0.1–1.7%) are greater than previously reported (0.07–0.13%). The presence of normal liver function tests in both those with significant liver disease (ranging from 41·0% to 74·6%) and those with cirrhosis (90·9% in one study) is a stark reminder of the limitations of these tests to detect chronic liver injury.	Four years ago, UK physicians highlighted the lack of clear pathway to diagnose and monitor patients with chronic liver disease and the lack of evidence to stratify those patients. As most of chronic liver diseases are silent disease until liver cirrhosis, it is clear that reliance on abnormal liver function tests will miss most patients with significant liver injury.
Rhodes, 2020, UK (4)	Among ALD referrals 147/229 (64.2%) had no evidence of advanced fibrosis and were judged 'unnecessary'. Advanced fibrosis was observed in men drinking ≥50 units per week (U/w) (OR 2.74, 95% CI 1.51 to 5, p=0.001) and ≥35 U/w in women (OR 5.11, 95% CI 1.31 to 20.03, p=0.019). Drinking >14 U/w doubled the likelihood of advanced fibrosis in overweight/obesity (OR 2.11; 95% CI 1.44 to 3.09; p<0.001). Use of fibrosis 4 score could halve unnecessary referrals (OR 0.50; 95% CI 0.32 to 0.79, p=0.003) with false-negative rate of 22%, but was rarely used.	This study reflects real-world experience of consecutive alcohol referrals from primary care to a specialist liver centre over a 3-year period. This study was led by the Royal Free Hospital, which is strongly involved in chronic liver management on the use of the use of non-invasive test. The inventor of the enhanced liver fibrosis (ELF) test, commercialized by Siemens, led the study.
El-Gohary, 2018, UK (3)	**Pathway 1**: Out of the 715 potential participants referred by GPs and practice nurses, 627 (87.7%) were invited into the study, and 272 (38.0%) took part. Half of this group had some evidence of liver disease (liver	Liver stiffness was measured using transient elastography with a portable FibroScan 402. This model is not available anymore in the UK. There is consistency with all our FibroScan systems (current and past) as they assess liver stiffness by transient elastography with the same technique

	warning 25.8%, progressive fibrosis 19.2%, probable cirrhosis 5.2%. **Pathway 2**: The majority of the randomly selected 4397 participants were identified due to abnormal blood tests (n = 2657), followed by diabetes (n = 942), CIRRUS algorithm (n = 665) and alcohol misuse (n = 163). 1235 (28%) participants were invited into the study with 465 attending. Nearly half showed some evidence of liver disease (47.9% in total–liver warning 24.8%, progressive fibrosis 17.4%, probable cirrhosis 5.8%). **Pathway 3**: Of 9510 AUDIT questionnaires sent out, 2071 were returned altogether (21.8% response rate). After exclusions due to insufficient score (<8), 220 participants were invited to clinic with 173 (79%) included in the study. Most (70.5%) did not have evidence of liver fibrosis, with 19.7% having a liver warning, 7.5% progressive fibrosis and 2.3% probable cirrhosis. Overall 910 cases had a validated liver diagnosis and were categorised: 44 (4.8%) probable cirrhosis, 141 (15.5%) progressive fibrosis, 220 (24.2%) liver warning and 505 (55.5%) with no evidence of liver fibrosis. Out of the 405 with a liver disease diagnosis, 136 (33.6%) were from a GP referral, 218 (53.8%) from the risk factor pathway with only 51 (12.6%) from the AUDIT mail out.	This study shows the increasing involvement of liver nurses "outside of the wall" with positive outcomes. Southampton area is one of the leader in building/experimenting liver pathway at a primary care level. The definition of the different cut-offs did not follow our official recommendations as cut-offs may vary, depending of the aetiology of the liver disease. The failure rate to measure elastography was low (1.9%)
Harris et al, 2019 (8)	Five hundred and seventy six patients participated in the pathway of which, 533 patients had a reliable reading and 66 (12.4%) had an elevated reading. Thirty	The patients included in this study are the same patients included in the Harman studies (7,9). They are part of the Nottingham Community Liver Biomarkers Cohort (NCT02037867).

	one percent of patients with an elevated reading had obesity as their only risk factor. The proportion of patients with an elevated reading was similar among those with obesity (8.9%) to patients with more recognised solitary risk factors (Type 2 diabetes 10.8%; Hazardous alcohol use 4.8%). Obesity in combination with other risk factors further increased the proportion of patients with an elevated reading. In multivariate logistic regression, increasing BMI and type 2 diabetes were significantly associated with an elevated reading.	The study included well-trained operators with more than 100 examinations each.
Harman et al, 2018 (9)	Two thousand three hundred and sixty eight patients were invited for transient elastography and 899/919 who attended (97.8%) had valid measurements. Of these 230 patients had elevated liver stiffness (25.6%) and 27 had cirrhosis (2.9%). Risk factors for new cirrhosis diagnoses were obesity and/or Type 2 diabetes in 16 patients (59.3%), alcohol alone in 3 (11.1%) and both alcohol and obesity and/or diabetes in eight (29.6%). Presence of cirrhosis was significantly increased in obese patients with Type 2 diabetes or hazardous alcohol use compared to non-obese (odds ratio 9.4 [95% CI 2.2-40.9] and 5.6 [95% CI 1.6-19.7] respectively).	The patients included in this study are part of the Nottingham Community Liver Biomarkers Cohort (NCT02037867).
Southampton Pilot study	Phase 1 of the pilot (UHS nurse to GP surgery 1/2/3 afternoons per month) October 2018 to Dec 2019 • 170 attended, 46 (21%) failed to attend (~20% typical historically) • 124 (73%) discharged back to GP, 46 (27%) referred to hepatology Phase 2 of the pilot continuing to business as usual (structured commissioned service delivered by a	Southampton City CCG develop and implement a community hepatology service to increase earlier detection, prevention and management of liver disease, and reduce unnecessary acute hospital activity. The community FibroScan, as part of the wider primary care liver pathway, reduces hospital first outpatient activity by >70%, and by following the correct work up also reduces follow up activity. As well as cost savings (community provider ~£127),

	community service, at service base plus GP surgeries) Jan 2020 to March 2021 • 533 attended, 66 (8.6%) failed to attend (patients called and text when offering appointment) • 407 (76.4%) discharge back to GP, 126 (23.6%) referred to hepatology	this has freed up capacity for the hospital to see patients who require secondary care intervention in a more timely way. Some outcomes are still pending and should be available in the economic evidence section.

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Embedding assessment of liver fibrosis into routine diabetic review in primary care. Mansour et al. JHEP Reports 2021.	
How are the findings relevant to the decision problem?	The pathway to identify significant liver fibrosis in patients with T2DM was developed as a service innovation in collaboration with General Practitioners and the Newcastle and Gateshead Primary Care Clinical Commissioning Group, and run as a pilot in 2 GP practices in Gateshead between April 2018 and September 2019 There was an almost 7-fold increase in the detection of advanced liver disease compared with standard care in place before the pilot (4.55% vs. 0.67% odds ratio [OR] 6.71, 95% CI 2.0–22.7 p = 0.0022). There were further significant changes in management as a result of the pathway The study found that patients were more likely to attend for TE at their local GP surgery than a hospital clinic. None of the patients offered the scan at their GP surgery failed to attend.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Performing a FibroScan procedure at a primary care level is more reassuring than going to the hospital for patients. As a result of the pathway, 20 new cases of advanced liver disease were identified from a cohort of 475 patients, representing almost a 7-fold increase from standard care in this cohort of higher risk patients with T2DM diabetes, including patients with dual aetiology (alcohol and metabolic) fatty liver disease. Almost half of patients subsequently diagnosed with advanced liver disease had a normal ALT level and would have been missed if only liver enzymes were used to identify liver disease. Conversely, only 1 in 5 patients with an abnormal ALT level were identified as having advanced liver disease.
Will any information from this study be used in the economic model?	Yes, as a prerequisite Some outputs of this study will be used to inform the economic model There is no requirement for pre-screening, and primary care teams are supported by prompts via patients' electronic medical records. This means that the pathway can be embedded into chronic disease monitoring and implemented by practice

	nurses and healthcare assistants, thus minimising strain on general practitioners. It also streamlines the patient journey, reducing the number of patient attendances to primary care, unnecessary referrals to secondary care and FibroScan testing uptake.
What are the limitations of this evidence?	As this was a pragmatic real-world study; GPs and secondary care clinicians were able to use their discretion as to which patients were referred for further investigations, and which were offered ongoing surveillance and follow-up. The number of liver biopsies performed was low and, whilst all patients diagnosed with 'advanced liver disease' had either histological, imaging, or endoscopic evidence of advanced disease, we were unable to make a definitive fibrosis assessment in 3/25 patients with LSM >8 kPa. The majority of patients offered a liver biopsy declined and opted for clinical follow-up or surveillance. This may change as the pathway becomes established and with the emergence of new treatments, but once again emphasises the importance of developing more reliable non-invasive biomarkers. As only patients with a Fib-4 score above the age-related cut-offs were referred for TE, the study may have missed patients with advanced disease who have a Fib-4 score below the age-related cut-offs.
How was the study funded?	The authors received no financial support to produce this manuscript

Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography. Harman et al. 2015 (7)	
How are the findings relevant to the decision problem?	Many patients referred for investigation of abnormal liver tests have no evidence of significant liver disease when investigated in hospital. In total, 5,922 adult patients (56.5%) had alcohol consumption documented, with 6.3% of the total GP population (658 patients) meeting our definition for hazardous alcohol use. The adult prevalence of type 2 diabetes was 3.7% (390 patients)
Does this evidence support any of the claimed benefits for the technology? If so, which?	Valid liver stiffness acquisition was possible in 366 patients (96.8%). A new diagnosis of clinically significant liver disease was made in 98 patients (26.8%) with valid TE measurement. This represents a substantial increase in diagnoses for these practices. The new observed cirrhosis prevalence of 19 patients after the study period therefore represents a 140% increase compared with before the study;

	usual care methods missed the majority of patients with very advanced liver disease. For local ALT cut-offs (>35 U/L for women and >45 U/L for men), 72.4% of patients with elevated liver stiffness, 60% with liver fibrosis on biopsy and 90.9% with liver cirrhosis had normal ALT levels, and would have been missed by standard diagnostic algorithms. This increase the rate of accurate diagnosis.
Will any information from this study be used in the economic model?	This study highlights outcomes such as incidence and severity of liver fibrosis as the main outcome is the diagnosis of clinically significant liver disease. Some outputs of this study will be used to inform the economic model
What are the limitations of this evidence?	The authors investigated patients from specific medical practices within a distinct sociodemographic area of the UK. It is possible that both patient attendance and the detection of clinically significant liver disease may differ elsewhere, and further study of our algorithm in other regions is necessary. The pragmatic study design, both in terms of biomarker selection and investigation of elected risk factors for liver disease, means they also cannot formally assess the sensitivity of the algorithm, or the total fibrosis and cirrhosis prevalence, in this community population Additional risk factors such as obesity and the metabolic syndrome, while incorporated partially in this pathway (eg, BARD score) were not specifically included, to ensure feasible stratification of the defined at-risk patient groups during the time of the study period. Taken together, the detected prevalence of significant disease, including cirrhosis, may represent an underestimate and the presence of cirrhosis in the community is likely to be higher than we report Patient uptake of screening was not optimal (55% of targeted patients were investigated with the algorithm).
How was the study funded?	Internal funding for study was provided by the NIHR Nottingham Digestive Diseases Biomedical Research Unit, part of the University of Nottingham and Nottingham University Hospitals NHS Trust. The study sponsor is the University of Nottingham, who are data custodians. The article presents independent research funded by the National Institute for Health Research (NIHR).

Prevalence of clinically significant liver disease within the general population, as defined by non-invasive markers of liver fibrosis: a systematic review. Harris et al. 2017 Lancet	
How are the findings relevant to the decision problem?	The authors have shown in this systematic review that several non-invasive tests have the ability to stratify for the severity of liver disease within a community setting? The participation of those invited suggests that as screening tests for the use in the community, non-invasive tests are more acceptable to patients. The prevalence estimates of cirrhosis (0.1–1.7%) are greater than previously reported (0.07– 0.13%) highlighting the burden of undiagnosed chronic liver disease. This systematic review shows that the long-standing reliance on liver function tests is misguided, and that current strategies are ineffective and missing a large proportion of patients with asymptomatic liver disease;
Does this evidence support any of the claimed benefits for the technology? If so, which?	The presence of normal liver function tests in both those with significant liver disease (ranging from 41·0% to 74·6%) and those with cirrhosis (90·9% in one study) is a stark reminder of the limitations of these tests to detect chronic liver injury. The use of a liver biopsy as a screening tool is not feasible because of the practicalities of doing an invasive procedure in a community setting, the expense, and the low prevalence of disease; together this results in an unfavourable risk–benefit ratio. Targeting patients with known risk factors will improve the diagnostic outcome and be more effective in identifying patients with asymptomatic chronic liver disease. FibroScan enables a liver test to be done non-invasively.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	The studies selected in this systematic review presented different patient selection, different liver disease risk factor (from not stated to hazardous alcohol use, obesity, type 2 diabetes, NAFLD, BMI > 30, etc.) with various sample sizes. This systematic review highlights that caution needs to be taken in extrapolating non-invasive markers for the detection of clinically significant liver disease, but greater agreement exists in the context of detecting liver cirrhosis.

How was the study funded?	The authors declare no competing interests. The paper presents independent research funded by the National Institute for Health Research (NIHR).

Is there scope to improve the selection of patients with alcohol-related liver disease for referral to secondary care? A retrospective analysis of primary care referrals to a UK liver centre, incorporating simple blood tests. Rhodes et al. 2020. BMJ Open	
How are the findings relevant to the decision problem?	The current referral strategy for patients with AUDs at risk of liver disease from primary care is inefficient and ineffective. Two-thirds of the patients referred to secondary care for suspected ALD had no evidence of advanced fibrosis, representing unnecessary referrals. This can be explained in part because the most common reasons for referral were abnormal LFTs and ultrasound scans, neither of which are sensitive or specific tests for advanced fibrosis.
Does this evidence support any of the claimed benefits for the technology? If so, which?	There is a need for improved collaboration between primary and secondary care services to develop referral pathways employing NIT, with evaluation to further refine thresholds for referral and education to improve awareness and the advice provided to patient about the impact of overweight/ obesity and alcohol on liver health. This shows that delivery of FibroScan examination in primary care rather than in secondary setting is manageable and requires less time.
Will any information from this study be used in the economic model?	This study highlights outcomes such as number of referrals from primary care to secondary care and incidence/ severity of liver fibrosis. Some outputs of this study will be used to inform the economic model
What are the limitations of this evidence?	This retrospective study lacked access to liver biopsy as a reference standard to stage fibrosis severity. Self-reported alcohol intake at the point of referral to secondary care was used to record drinking behaviour and this may not be reliable. This was a retrospective study relying on data held in electronic clinical records, including of self-reported alcohol intake. The study used consensus judgement of expert hepatologists to assess liver disease rather than liver biopsy as a reference standard to assess fibrosis severity.
How was the study funded?	This study is being supported by funding from WR's National Institute for Health Research (NIHR) Senior Investigator Award (award number 200249). WR is an NIHR Senior Investigator and is supported by the NIHR University College London

	Hospitals Biomedical Research Centre. JP-G was supported by the UK NIHR Applied Research Collaboration North Thames (ARC North Thames) at Bart's Health NHS Trust.

Local care and treatment of liver disease (LOCATE) – A cluster-randomized feasibility study to discover, assess and manage early liver disease in primary care. El Gohary. 2018.	
How are the findings relevant to the decision problem?	This study aimed to assess the feasibility in primary care of different approaches in identifying subjects with progressive liver disease. The modalities used were unique in the sense that this is the first study to have been carried out using both a non-invasive fibrosis marker panel (STL) and transient elastography together, culminating in nearly half of the participants having a degree of chronic liver disease including 20.3% with progressive fibrosis or cirrhosis. Almost all participants were seen at their usual GP practice, with valid and reliable elastography measurements. This approach allowed the majority of participants to be managed within the community with appropriate referral if required.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The incorporation of a liver health nurse into GP practices was simple to arrange and yielded a much higher number of new diagnoses of liver disease compared to usual care. Nurse led case finding and GP referrals were most effective compared to AUDIT questionnaire for patients with alcohol liver disease. The use of non-invasive tests for the diagnosis and management of patients with suspected chronic liver disease showed relevant use at a primary care level and across different tested patient pathways. Once the study was up and running, the authors were assessing approximately 50 new subjects / month with two WTE nurses and less than half a consultant session. It was possible to ascribe a liver fibrosis stage in all subjects, and a disease aetiology in more than 98%.
Will any information from this study be used in the economic model?	This study highlights outcomes such as incidence and severity of liver fibrosis as the main outcome is the diagnosis of clinically significant liver disease.

	Some outputs of this study will be used to inform the economic model
What are the limitations of this evidence?	There were some differences within the baseline characteristics of the intervention and control practices. This is likely due to an increased student population in one of the intervention practices. The authors also did not subject any of the participants to a liver biopsy due to the pragmatic design of the study and so we do not have any histological diagnoses to back up our investigative results. This was a study focused on enhancement of identification of disease, i.e. diagnosis, we have not been in a position to follow up participants longitudinally and are therefore unable to comment on if such early diagnoses translate into better outcomes.
How was the study funded?	Funded by British Liver Trust: Registration Study ID 14131. National Institute for Health Research - In-Practice Fellowship - Personal award for ME-G. School for Primary Care Research – Personal award for ME-G. National Institute for Health Research - Biomedical Research Centre at Southampton University Hospitals NHS Trust. Awarded to NS. Consultancy work and travelling expenses from the pharmaceutical companies: Norgine (2014) and Kyowa Kirin Limited (2014), Gilead 2018. Granted to NS.

Obesity is the most common risk factor for chronic liver disease: Results from risk stratification pathway using transient elastography. Harris et al, 2019	
How are the findings relevant to the decision problem?	The study confirmed that obese patients (defined as a BMI > 30) are at-risk regarding chronic liver disease. These patients are mostly followed within a primary care setting and without dedicated liver investigations. The study showed that 12.8% of these patients had a liver stiffness measurement above 8 kPa, which is surrogate biomarker for advanced liver fibrosis. All patients with an elevated reading were invited back to see a hepatologist (employed by the university hospital) in the primary care practice.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The study confirms obesity but also T2DM and hazardous alcohol use as risk-factors for chronic liver disease.

	It also shows that when invited by their primary care centre, there is a strong uptake from eligible patients to undergo a FibroScan examination based on their conditions and this increases compliance with the FibroScan examination. Patients below a liver stiffness < 8 kPa remains in the primary care setting for regular follow-up whereas the patients > 8kPa are invited to see a consultant hepatologists for further investigation.
Will any information from this study be used in the economic model?	This study highlights outcomes such as eligible patients to be included in the pathway (at-risk patient with high BMI).
What are the limitations of this evidence?	Based on patient's inclusion criteria, the authors were not able to determine the risk of chronic liver disease within the general population. There might be a bias as the patients attending the study may not be representative of the whole spectrum of those within the at risks groups. Identification of patients from the routine electronic primary care records is only as useful as the accuracy of the data recorded within it. Some conditions could mislead FibroScan examination interpretation (i.e cholestasis, congestive cardiac failure, etc.). Finally, as the study was conducted in the primary care setting, histological data from liver biopsy were not available to confirm the diagnosis of advanced fibrosis or cirrhosis.
How was the study funded?	Funding for study was provided by i) the Nottingham Digestive Diseases Centre and National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre part of the Nottingham University Hospitals NHS Trust and University of Nottingham and ii) The East Midlands Academic Health Sciences Network (EMAHSN).

Obesity and type 2 diabetes are important risk factors underlying previously undiagnosed cirrhosis in general practice: a cross-sectional study using transient elastography. Harman et al. 2015 (9)	
How are the findings relevant to the decision problem?	Patients with elevated liver stiffness results, including high but unreliable acquisitions, were reviewed by a visiting consultant hepatologists in the community in the course of a local liver pathway. 27/230 patients with elevated liver stiffness were newly diagnosed with liver cirrhosis during the study period (3% of valid liver stiffness results). This, therefore, more than doubled the number of

	cirrhosis diagnoses in the studied general practices.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The study enable early diagnosis of liver cirrhosis in the primary care setting. Patients would not have been identified before late stage cirrhosis and hospital stay
Will any information from this study be used in the economic model?	This study highlights outcomes such as confirmed risk-factors such as T2DM and hazardous alcohol use for advanced fibrosis and cirrhosis
What are the limitations of this evidence?	One of the limitations however is that only 45% of the eligible population underwent the transient elastography examination, although this is a greater response rate than the other major UK primary care liver stratification study thus far reported. There was however a response bias with screening attenders being older, more female and with a differing proportion of hazardous alcohol use and Type 2 diabetes than non-attenders. A further limitation is that as we targeted only Type 2 diabetes and alcohol misuse as risk factors, though we have been able to show that obesity is an important co-factor in each.
How was the study funded?	Funding for study was provided by 2 sources (1) the NIHR Nottingham Biomedical Research Centre, part of the University of Nottingham and Nottingham University Hospitals NHS Trust and (2) The East Midlands Academic Health Sciences Network (AHSN). The study sponsor is the University of Nottingham, who is data custodians but had no role in the design, analysis or interpretations of the data.

Southampton Pilot Study: Community Hepatology Service Pilot Proposal	
How are the findings relevant to the decision problem?	The Community FibroScan pathway is a key part of a wider Southampton liver pathway which is seeking to increase earlier detection and timely intervention and management of patients with and at risk of liver disease
Does this evidence support any of the claimed benefits for the technology? If so, which?	The first phase of the pilot demonstrated proof of concept of GP direct access to FibroScan and care closer to home. Learning from it has shaped the delivery model for this second phase. This new service will continue to deliver the benefits realised in the first phase, offer improved access, and support modelling for the commissioning of a future Community Hepatology Service.

	Results between the phase 1 and the phase 2 showed an increase in the uptake of the FibroScan examination (from 21% to 8.6% of patients who failed to attend)
Will any information from this study be used in the economic model?	Some inputs and outputs of this study will be used to inform the economic model
What are the limitations of this evidence?	We had very limited access to the data so we cannot conclude on the limitations of the evidence.
How was the study funded?	The pilot was funded by the Southampton City CCG

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

The FDA MAUDE database was screened on Jan-2020. The keyword “Fibroscan” was searched within the category “brand name” without date restriction (results available in the last clinical evaluation report).
However, no events were found as a result of this search.
No complication is known to date. The FibroScan operates with low-power ultrasound.

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

No adverse events were described in the clinical evidence.

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

Evidence synthesis was suitable for aggregating the results on the cohort and cross-sectional studies on 1 outcome, the diagnosis rate of advanced fibrosis.
We performed the meta-analyse and forest plots using a Microsoft Excel spreadsheet as described in the Neyeloff et al study from 2012 (10).

Populations

The 6 included studies encompassed a limited range of aetiologies, including patients with type 2 diabetes, patients with hazardous alcohol use, obese patients (defined as a BMI > 30 kg/m²), patients with NAFLD and patients with elevated liver functions tests. All 6 studies included adult populations.

Interventions

All studies assessed the use of FibroScan in primary care. Additional non-invasive tests were performed such as FIB-4 in 3 studies (2,4,7), liver function tests in 3 studies (2,3,7) and other less used tests such as APRI (2), BARD Score (7) and the Southampton traffic light test (3). Liver stiffness measurement (in kPa) was available in all studies.

Comparators

Only one study compared 3 different pathways (3).

Outcomes

The outcomes are presented in the table below.

Study	Results	OR values	TE thresholds	TE valid measure rate
Mansour, 2021	82/466 (17.7%) have FIB-4 > 1.3 58/466 (12%) referred for TE 25/58 (43%) have LSM > 8 kPa	Alcohol (OR 1.05 [1.02–1.08] p = 0.001) and BMI (OR 1.09 [1.01–1.17] p = 0.021) were predictors of AF 20/ 440 (4.5%) patients were found to have AF following specialist review, compared to 3 patients previously identified through standard care ([OR] 6.71 [2.0–22.7] p = 0.0022).	> 8 kPa for advanced fibrosis	90.7%
Rhodes, 2020	147/229 (64.2%) patients with ALD had no evidence of advanced fibrosis and could be considered "unnecessary" referrals 443/531 (83.4%) patients with NAFLD had no evidence of advanced fibrosis.	AF was observed in men drinking ≥50 units per week (U/w) (OR 2.74, 95% CI 1.51 to 5, p=0.001) and ≥35 U/w in women (OR 5.11, 95% CI 1.31 to 20.03, p=0.019). Drinking >14 U/w doubled the likelihood of advanced fibrosis in overweight/obesity (OR 2.11; 95% CI 1.44 to 3.09; p<0.001).	> 10 kPa for NAFLD for advanced fibrosis > 11 kPa for ALD for advanced fibrosis	91%
Harman, 2015	378 patients underwent TE 98 patients were newly diagnosed with valid TE measurement		> 8 kPa	96.8%
Harman, 2018	899 successfull LSM results 230/899 had LSM ≥ 8 kPa 27/230 (11.7%) newly diagnoses with liver cirrhosis	Presence of cirrhosis was significantly increased in obese patients with T2DM (odds ratio 9.4 [95% CI 2.2-40.9]) ALD compared to non-obese and 5.6 [95% CI 1.6-19.7] respectively).	> 8 kPa	97.8%
El-Gohary, 2018	544 incidents cases identified in the intervention arm vs. 221 (OR: 2.4, 95%CI [2.1-2.8]) Amongst the 544 incidents, 141/910 (15.5%) cases has progressive fibrosis (19.2% in pathway 1, 17.4% in pathway 2 and 7.5% in pathway 3)		>8 kPa for progressive fibrosis	98.1%
Harris, 2019	66/533 (12.4%) of patients had a TE reading ≥ 8kPa; of the patients who had obesity 8.9% has a TE reading ≥ 8kPa	BMI between 30-34.9 kg/m2 TE reading ≥8.0 kPa was 8.40 (95% CI 0.80-88.41; p value = 0.076) T2DM + BMI between 30-34.9 kg/m2 the odds of a having a TE reading ≥8.0 kPa (OR = 5.24, 95% CI 1.21-22.69, p value = 0.027)	> 8.0 kPa	93%

We also identified one systematic review done by Harris et al within the literature review (1). We decided to present it in this section as it can be of interest (more robust methodology and published in a peer-reviewed journal).

Methods

This systematic review was done in accordance with the Cochrane Handbook for Systematic Reviews of Interventions17 and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Two reviewers (RH and DJH) defined the key MeSH headings and free text search terms relevant to the participants involved in the studies, the two causes of chronic liver disease, the community setting, and the non-invasive tests used to stratify for liver fibrosis.

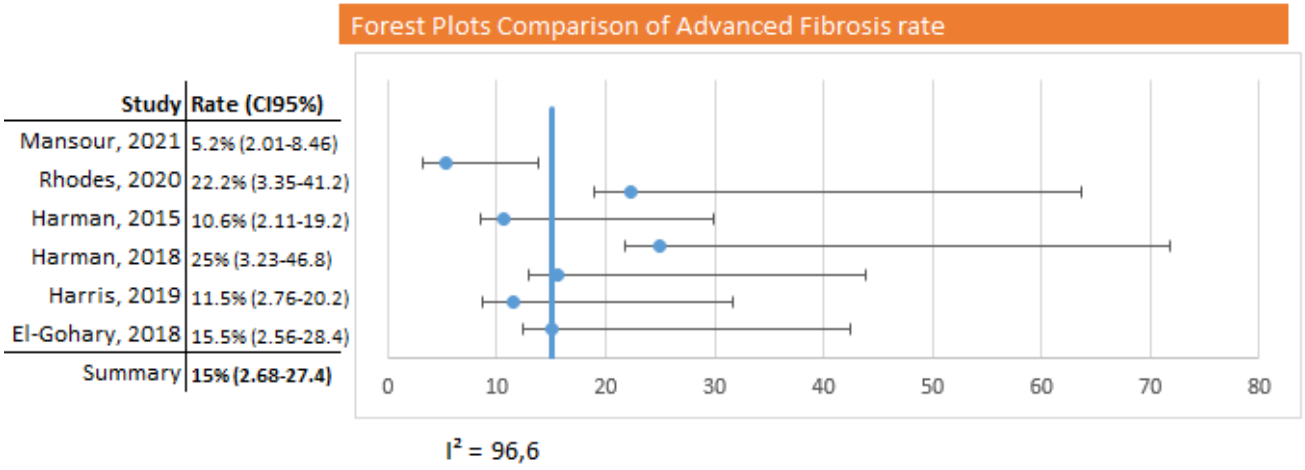
The titles and abstracts of all studies identified in the literature search were screened to determine their suitability for inclusion. The full texts of all studies considered to be suitable were assessed for eligibility. Any disagreements were discussed but, if these could not be resolved, advice from a third reviewer (ING) was sought.

Selection Criteria

- Studies were included if the study was done in adults aged 18 years or older;
- Study population was from a non-hospital setting (eg, community, primary care, or outreach unit);
- Study participants underwent a validated non-invasive test, which would stratify for liver fibrosis; the prevalence of clinically significant liver disease, either liver fibrosis or cirrhosis, was reported as an outcome measure by the study;
- Study participants were recruited from an unselected population or on the basis of the participants' age, or a defined risk factor for ALD disease or NAFLD

Report all relevant results, including diagrams if appropriate.

The graph below presents the forest plots using a Microsoft Excel spreadsheet on the diagnosis rate of advanced fibrosis (outcomes available in 6 studies).



The results of the evidence synthesis show that the diagnosis of advanced fibrosis was positive in 15% of patients from 6 studies. These results should be interpreted with caution due to the coefficient of heterogeneity.

Harris et al meta-analysis (1):

19 studies were included in the systematic review

10/19 studies reporting liver fibrosis prevalence in unselected participants or participants selected by age alone with the use of a non-invasive test in a community setting

7/19 studies reporting liver cirrhosis with the use of a non-invasive test in a community setting

Screening uptake: The proportion of patients that participated in screening from the invited study population was reported in eight studies, and ranged from 20% to 89%

The 19 studies reported prevalence of fibrosis from 2.0% to 19.0%, but only 11/19 studies reported prevalence of cirrhosis from 0.1% to 4%.

Regarding patients stratifications, 10/19 studies identified patients to be at-risk of NAFLD with prevalence of fibrosis from 0% to 92,6%, 4/19 studies identified patients to be at-risk of ALD with reported prevalence of fibrosis between 11.0% and 20.5%.

Concerning liver disease risk factors, 7/19 were unselected (but 2/7 with subgroup analysis: alcohol and NAFLD), 3/19 were on age, 4/19 were on NAFLD, 2/19 were on T2DM and 2/19 were on alcohol consumption.

Transient elastography as a non-invasive test was used in 12/19 studies on 14,346 patients screened.

There was substantial heterogeneity in the community studies included for analysis, so forest plots were not calculated and the authors did not pool effect sizes to calculate T^2. The authors did not assess the degree of heterogeneity within the pooled studies to calculate I^2

Explain the main findings and conclusions drawn from the evidence synthesis.

The authors have shown in this systematic review that several non-invasive tests have the ability to stratify for the severity of liver disease within a community setting.

Even though, the variation in reported disease prevalence highlights the uncertainty about which test is most appropriate, there is an increasing use of FibroScan in primary care with data on several thousands of patients, including UK patients.

The UK is leading the way in these pilots/studies to highlight the relevance of using FibroScan in liver pathway starting in primary care.

The participation of those invited suggests that as screening tests for the use in the community, non-invasive tests are more acceptable to patients.

The prevalence estimates of cirrhosis (0·1–1·7%) are greater than previously reported (0·07–0·13%) highlighting the burden of undiagnosed chronic liver disease in the general population

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

The evidence reported in the previous section shows the value of FibroScan in terms of enabling earlier and accurate diagnosis, enabling a test to be done non-invasively in a primary care setting (or outside the secondary care setting), by avoiding unnecessary referrals of patients to secondary care and increased compliance of patients.

We selected only UK studies in order to be generalizable to the NHS population. As the number of UK based studies is significant, we decided to exclude non-UK studies.

The clinical evidence base relating to FibroScan in primary care is relatively high quality in the methodology despite the lack of comparative study and also the lack of formal validated liver pathway at a UK country level.

The cohort and cross-sectional studies enrolled more than 4,500 patients in total. The population enrolled and procedure were consistent with the same aetiologies: type 2 diabetes, obesity, hazardous alcohol use and NAFLD. The outcomes that were consistently reported were the rate of valid measure, the diagnosis rate of advanced fibrosis and/or cirrhosis (with consistent cut-off from 8.0 kPa to 10 kPa depending of the conditions).

Early and accurate diagnostic of advanced fibrosis in the primary care setting

The FibroScan examination was performed in a primary care setting in all the studies. Valid measure rate was available in all studies and lies between 90% and 98%. No side effects, complications or risks were identified.

The rate of advanced fibrosis was from 5.2% [CI95%: 2.01-8.46%] to 25% [CI95%: 3.23-46.8] depending of the population (from general population to at risk patients [T2DM, hazardous alcohol use, obesity, NAFLD, etc.]).

Correlation between aetiologies and advanced fibrosis

The link between hazardous alcohol use and advanced fibrosis was highlighted in 4 studies (2,4,7,9) whereas the link between metabolic conditions (T2DM, NAFLD, obesity) was highlighted in 5 studies (2,4,7–9) with statistically significant OR values.

Increases compliance

Patients feel more confident to have a FibroScan examination within a primary care setting as we see an increasing uptake (100% of patients attended in primary care instead of 94% in secondary care (2)).

The role of liver nurses in primary care will be key to increase compliance for patients with chronic liver diseases and/or at-risk factors to have a FibroScan examination. El Gohary et al presents a feasibility study of a cluster randomised trial to evaluate whether incorporating liver health nurses in GP practices improves the identification of progressive liver disease compared to usual care. It tests the feasibility of practice recruitment, patient identification by different routes, uptake of nurse assessment and non-invasive liver testing (3).

The rate of compliance to attend a FibroScan examination was shown to be higher in primary care in the Southampton Pilot.

Unnecessary referrals

The referral outcome was highlighted in 1 study. Among the cohort of patients with ALD referred to secondary care, 35.81% were judged to have advanced fibrosis and thus 64.2% could be considered 'unnecessary' referrals (4).

No adverse events were reported within the body of clinical evidence.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

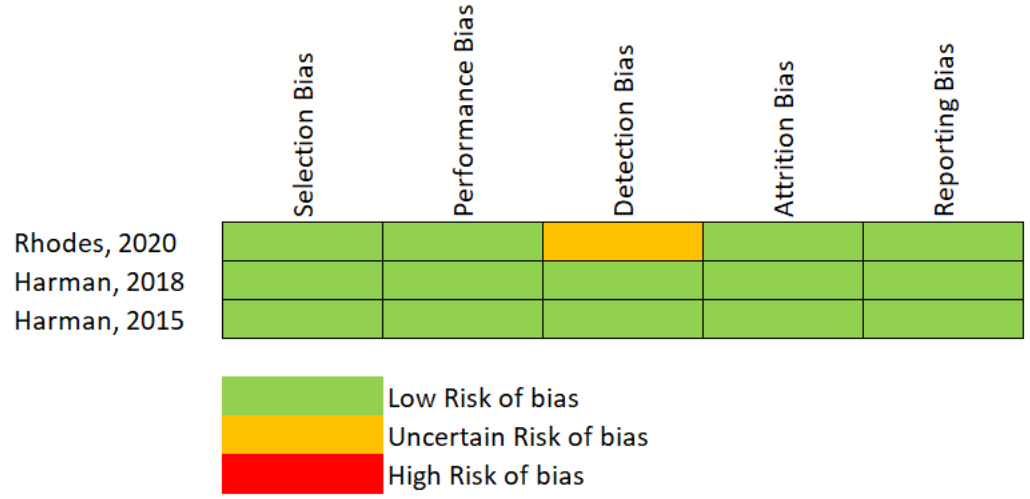
The evidence base relevant to the scope is limited when considering comparative data and randomized clinical trials. The large majority of the evidence is cohort or cross-sectional studies.

The cohort and cross-sectional studies have been found to be of consistent quality due to the overall clear reporting of data and important sample sizes (from 475 to 920 patients included). The population for the FibroScan examination is consistent within the different studies (T2DM, alcohol use, obesity, NAFLD etc.) so the studies included participants who had reasons to be suspected of having liver fibrosis or cirrhosis.

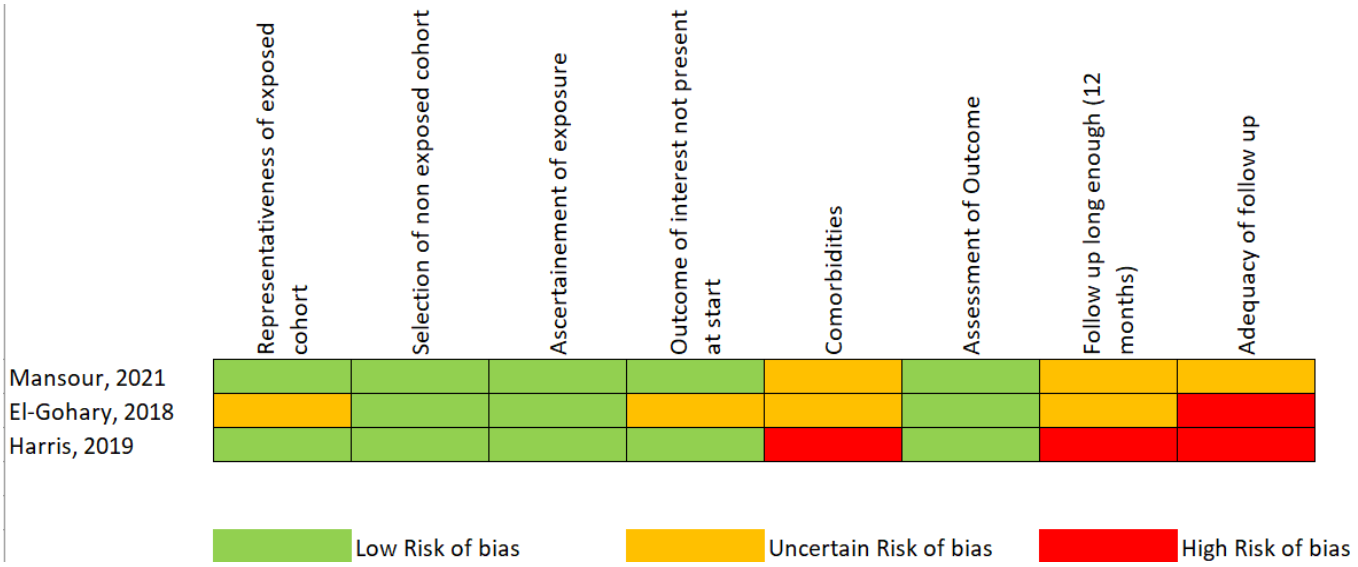
We acknowledge the need for comparative studies to compare different liver pathways in the UK NHS in order to facilitate a more robust assessment of the FibroScan in the primary care setting which may be possible with increase uptake of the device.

We conducted a review of risk bias, below the summary for cohort studies and cross-sectional studies

Cross-sectional studies.



Cohort studies.



Despite so heterogeneity in the quality of the selected studies, we are confident that they can support the claimed benefit described in the scope.

The table below summarizes the overall results of the individual studies.

Study	Country	Design	# Patients	Etiologies	Settings	Outcomes	Interventions	Results	OR values	TE thresholds	TE valid measure rate
Mansour, 2021	UK	Prospective non comparative study	475	T2DM	2 GP Practices	Number of patients with AF/LC identified	LFTs FIB-4 TE	82/466 (17.7%) have FIB-4 > 1.3 58/466 (12%) referred for TE 25/58 (43%) have LSM > 8 kPa	Alcohol (OR 1.05 [1.02–1.08] p = 0.001) and BMI (OR 1.09 [1.01–1.17] p = 0.021) were predictors of AF 20/ 440 (4.5%) patients were found to have AF following specialist review, compared to 3 patients previously identified through standard care ([OR] 6.71 [2.0–22.7] p = 0.0022).	> 8 kPa for advanced fibrosis	90.7%
Rhodes, 2020	UK	Retrospective cross-sectional analysis	762	NAFLD ALD	Primary Care	Rate of new patients referred from GP to HEP clinic with AF being "necessary referrals"	FIB-4 APRI TE	147/229 (64.2%) patients with ALD had no evidence of advanced fibrosis and could be considered "unnecessary" referrals 443/531 (83.4%) patients with NAFLD had no evidence of advanced fibrosis.	AF was observed in men drinking ≥50 units per week (U/w) (OR 2.74, 95% CI 1.51 to 5, p=0.001) and ≥35 U/w in women (OR 5.11, 95% CI 1.31 to 20.03, p=0.019). Drinking >14 U/w doubled the likelihood of advanced fibrosis in overweight/obesity (OR 2.11; 95% CI 1.44 to 3.09; p<0.001).	> 10 kPa for NAFLD for advanced fibrosis > 11 kPa for ALD for advanced fibrosis	91%
Harman, 2015	UK	Cross-sectional study with recruitment	920	T2DM ALD	2 GP Practices	Diagnosis of clinically significant liver disease	LFTs FIB-4 BARD Score TE	378 patients underwent TE 98 patients were newly diagnosed with valid TE measurement		> 8 kPa	96.8%
Harman, 2018	UK	Cross-sectional study with recruitment	919	T2DM ALD Elevated LFTs	4 GP Practices	To screen at-risk individuals in general practice for undetected cirrhosis	TE	899 successfull LSM results 230/899 had LSM ≥ 8 kPa 27/230 (11.7%) newly diagnoses with liver cirrhosis	Presence of cirrhosis was significantly increased in obese patients with T2DM (odds ratio 9.4 [95% CI 2.2-40.9]) ALD compared to non-obese and 5.6 [95% CI 1.6-19.7] respectively).	> 8 kPa	97.8%
El-Gohary, 2018	UK	Prospective cluster randomised feasibilty study	910	T2DM/Obesity ALD	10 GP Practices	Number of patients with AF/LC identified	Southampton Traffic light test Blood Tests AUDIT Questionnaire TE	544 incidents cases identified in the intervention arm vs. 221 (OR: 2.4, 95%CI [2.1-2.8]) Amongst the 544 incidents, 141/910 (15.5%) cases has progressive fibrosis (19.2% in pathway 1, 17.4% in pathway 2 and 7.5% in pathway 3)		>8 kPa for progressive fibrosis	98.1%
Harris, 2019	UK	Prospective study	576	T2DM Alcohol Obesity	1 GP Practice	Assess the effect of raised BMI on liver disease	LSM	66/533 (12.4%) of patients had a TE reading ≥ 8kPa; of the patients who had obesity 8.9% has a TE reading ≥ 8kPa	BMI between 30-34.9 kg/m2 TE reading ≥8.0 kPa was 8.40 (95% CI 0.80-88.41; p value = 0.076) T2DM + BMI between 30-34.9 kg/m2 the odds of a having a TE reading ≥8.0 kPa (OR = 5.24, 95% CI 1.21-22.69, p value = 0.027)	> 8.0 kPa	93%

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

All the submitted studies are UK based in order to give an overview of the ongoing practices within the UK NHS. As there is no official liver pathway validated at a national level, this explain the heterogeneity of the presented pathways. However, it is a appropriate overview of the current state of the art for patients with liver disease routine care

The factors that could vary between the current liver pathways are the inclusion criteria for patients recruitment/inclusion (general population or known risk factors such T2DM, alcohol use, metabolic syndrome) and the cut-offs for advanced fibrosis.

Some local teams within GP Practices can choose to also include viral hepatitis known patients as viral hepatitis (mostly Hep B and Hep C) can lead to advanced fibrosis and cirrhosis.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

As shown in the studies presented above, people the most at-risk for chronic liver diseases are patients with the following risk factors: type 2 diabetes mellitus, hazardous alcohol use, metabolic syndrome, NAFLD and obesity.

Patients with the above-mentioned conditions should be considered eligible to enter within a liver pathway that includes non-invasive tests such FIB-4, followed by transient elastography (FibroScan) at a primary care level if the FIB-4 score is > 1.3.

Indeed, the studies presented above demonstrated that standard liver function tests (AST, ALT and GGT) are not sufficient markers to identify liver disease (45% of patients with advanced liver disease had normal (2).)

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

All the study included patients with relevant risk factors, within the primary care settings in a single or multiple GP Practices in the UK

The success rate of the FibroScan procedures were high (from 82.3% to 99%) despite the fact that the level of experience of the operators was not systematically described. Moreover, some of the studies showed a higher uptake from patients to have a FibroScan procedure within a primary care setting than at the hospital.

The large majority of the evidence included studies led at a local level (maximum 10 GP surgeries within the same CCG) which also explained the heterogeneous inputs and outputs.

As only a few FibroScan are available in primary care (mostly a FibroScan from a hospital in the same CCGs than the primary care centres), the body of evidence (number of available data and study design) is increasing but not as consistent as it is for the use of FibroScan within secondary/tertiary care.

One of the other limitations was the lack of access to histological diagnostic data from liver biopsies as reference standard to back up the diagnosis of advanced fibrosis and liver cirrhosis.

9 References

Please include all references below using NICE's standard referencing style.

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10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	2021/08/15
Date span of search:	2004/01/01-3000/12/31

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

There are over 2,500 published studies on the use of FibroScan including recent reviews on its use in hepatitis C, hepatitis B and liver fibrosis in secondary care (NICE MIB216, 2020). FibroScan in secondary care is supported by the evidence and is widely used in the NHS. The search strategy will then only consider the technology in primary care.

Search Topic		**Search quary with filters**	**Results**
		PubMed	**PubMed**
Clinical Evidence			
1	Technology and condition	("FibroScan"[Tiab] OR "Vibration Controlled Transient Elastography"[Tiab] OR "Transient Elastography"[Tiab]) AND ("liver"[MeSH Terms] OR "liver"[All Fields] OR "liver fibrosis"[tiab] OR "liver cirrhosis"[tiab]) AND ("2004/01/01"[PDAT] : "3000/12/31"[PDAT])	3'209
2	Technology, condition and setting	("FibroScan"[Tiab] OR "Vibration Controlled Transient Elastography"[Tiab] OR "Transient Elastography"[Tiab]) AND ("liver"[MeSH Terms] OR "liver"[All Fields] OR "liver fibrosis"[tiab] OR "liver cirrhosis"[tiab]) AND ("primary care"[tiab]) AND ("2004/01/01"[PDAT] : "3000/12/31"[PDAT])	53
3			

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

No searches of company or professional organisation databases were conducted for this literature review.

Searches for guidelines and consensus recommendations were conducted on transient elastography as specified below

Keywords	Limits/Filters	Results			
		Food and Drug Administration	French Authority of Health (HAS)	National Health Service (NHS)	National Institute for health and Care Excellence (NICE)

Transient Elastography	Guidelines or recommendations	0	1	1	1

EASL: EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update

HAS: DIAGNOSIS OF UNCOMPLICATED CIRRHOSIS, 2008

NICE: MedTech Innovation Briefing MIB 216: FibroScan for assessing liver fibrosis and cirrhosis in primary care

Inclusion and exclusion criteria:

Inclusion criteria:

- Clinical data related to FibroScan
- Setting is primary care
- Data related to the intervention, clinical condition, purpose, specific characteristics and features of FibroScan
- UK based
- Data related to the same within the same site of the body: *non-invasive diagnostic tool for liver disease*
- Data related to the same patient population for which the devices are intended: adult and pediatric patients, on large sample size (at least 100 patients, except for pregnant women, for whom any clinical data identified on this population will be considered whatever the sample size).
- Data involving humans

Exclusion criteria:

- Different device
- Different indication
- Non-UK studies
- Methodology (inappropriate number of patients, case reports, final conclusions not available)
- Pre-clinical studies
- No abstract available
- Non peer-reviewed journal
- Technical notes
- Language other than English
- Duplicate of references

Data abstraction strategy:

We used a data abstraction form that included the following categories: study country, study design, number of patients, aetiologies, care setting, outcomes measured, interventions, results, thresholds for advanced liver fibrosis and valid measure rate.

Appropriate baseline data specific to each clinical indication was also considered.

One author independently performed data abstraction using this form, with results being compared after completion of document review.

Potential disagreements in abstracted elements were settled through involvement of Echosens Chief Medical Officer.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

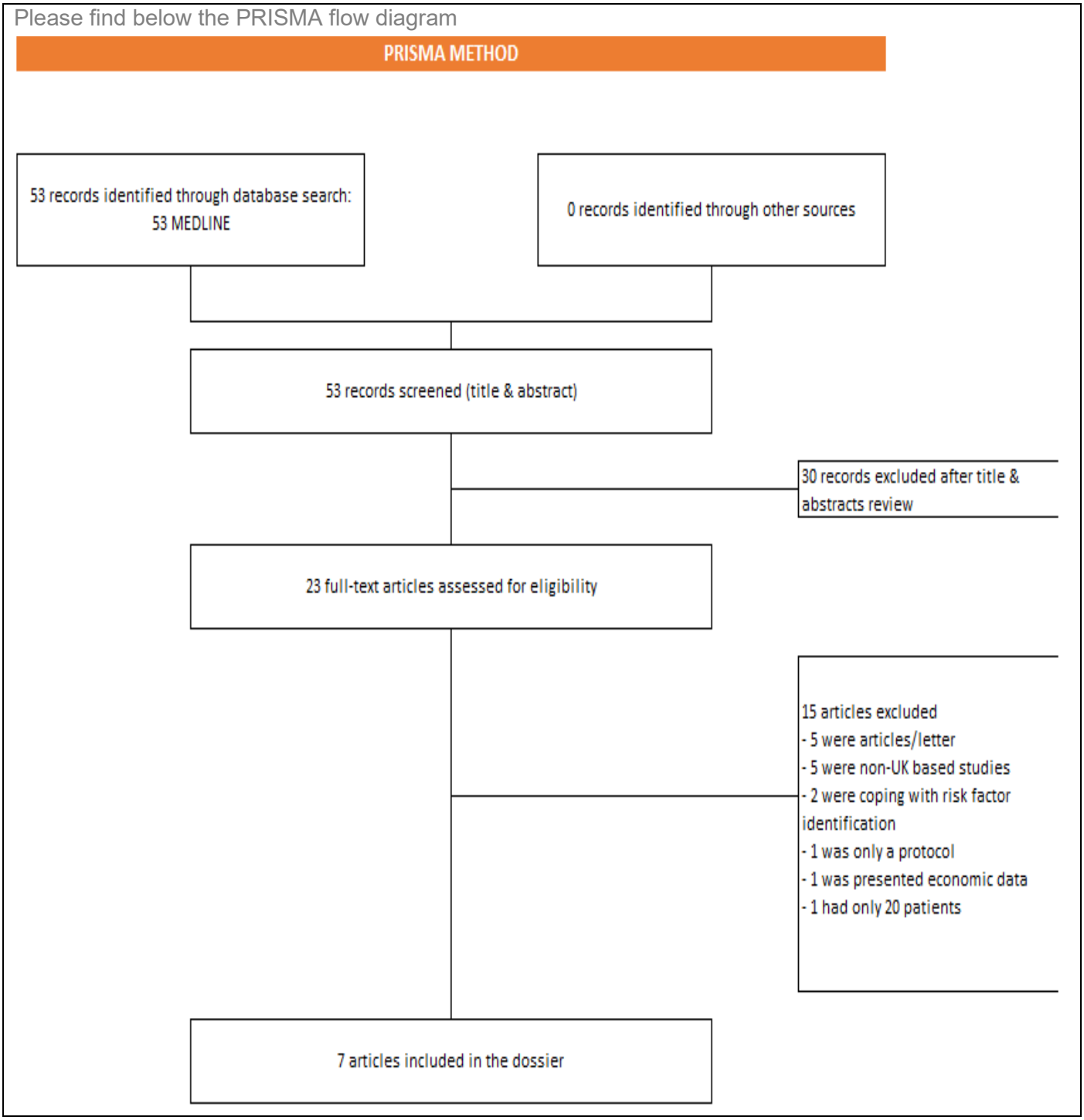
Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Nasr et al (11)	Prospective cohort study Intervention: Evaluate liver fat content using • MRI • MR-Elastography • Transient Elastography	Only a protocol	The study does not present relevant data at this stage. However, it will be interesting to have the data once the study will be completed
Yang et al (12)	Not applicable	This is not a study, it is journal article/ letter	No comment
Younossi et al. (13)	Prospective cohort study Intervention Non-invasive tests in primary care (APRI, NFS and FIB-4) and then FibroScan in secondary care to detect high-risk patients	US based study based on electronic health records and FibroScan procedure was not performed in a primary care setting (only 103/7,555 patients underwent transient elastography).	Zobair Younossi is a world known KOL specialised in NAFLD.
Boursier et al. (14)	Not applicable	This is not a study, it is journal article/ letter	No comment
Trivedi et al (15)	Retrospective study Intervention • Transient Elastography • CAP	US based study, retrospective study based on electronic health record Primary care healthcare teams were only allowed to order a FibroScan procedure for their patients. They were educated on the appropriate indications for FibroScan referrals but did not performed the procedure.	This study collected data on liver stiffness measurement and CAP only for patients with T2DM, obesity and metabolic syndrome. The referrals were done only on an initial known conditions basis with no triage by other NITs prior to FibroScan.
Vieira Barbosa et al (16)	Not applicable	This is not a study, it is journal article/ letter	No comment

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Pallini et al (17)	Not applicable	This is not a study, it is journal article/ letter	No comment
Knight et al (18)	Qualitative process evaluation with semistructured interviews Intervention • Transient elastography	This study includes only 20 patients, below the threshold of 100 patients from the inclusion criteria	It is complicated to interpret results and make conclusion on a sample of that size. However, this study provides interesting insights from a qualitative standpoint.
Chen et al (19)	Cross-sectional study Intervention • Transient Elastography • CAP • Liver function test (ALT, AST and platelet).	Despite the primary care setting (primary care clinic or diabetic centre), the patients are not included in a specific liver pathway and there is not mention a linkage between primary and secondary care settings. The purpose of this study was to assess the prevalence, clinical spectrum and risk factors of NAFLD and liver fibrosis among T2DM patients. It was a Singapore based study.	We wanted to focus the selected studies on pathways including primary and secondary care settings plus UK based studies. The decision tree considering only CAP for a diagnostic of NAFLD and then measure liver stiffness for advanced liver fibrosis is questionable and not part of Echosens recommendations.
Serra-Burriel et al (20)	Cost-effectiveness analysis with ICER calculation Intervention • Blood tests • Transient Elastography	This CE study is based on 6 different cohorts of patients. There is on cohort from the UK (378 patients). This is the same cohort from the Harman et al study from 2015 (7). There are discrepancies between the patient characteristics of the cohorts (age, etiologies , at-risk vs. general population) but also on patient pathways. The rate of missing values was 6%. This study will presented in the economic evidence section.	This study is part an EIT Health Project and funded by a grant within the LiverScreen Consortium. LiverScreen is a group of institutions from Europe that have the objective of investigating population-based screening for chronic liver diseases. This study is part of the work package dedicated to economic evidence.
Fabrellas et al (21)	Population-based, cross-sectional study Intervention • Blood tests • CAP	This study presents only CAP data as a surrogate marker for liver steatosis to assess the prevalence of hepatic steatosis. Liver stiffness was measured but the results cannot be interpreted as the authors 2 different cut-offs for the M	This study is one of the rare focusing liver disease assessment with CAP only as a surrogate marker for liver steatosis.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
	• Transient Elastography	and the XL probe which is against Echosens recommendations. This is a Spanish-based study.	
Sanyal et al (22)	Not applicable	This is not a study, it is journal article/ letter	No comment
Patel et al (23)	Survey	This is a survey among primary care clinicians to assess their approach to diagnosis, management and referral of NAFLD patients. This is an-Australian based study.	No comment. However, this study provides interesting insights from a qualitative standpoint.
Davyduke et al 2019 (24)	Retrospective study based on prospectively collected data Intervention • Blood Tests • FIB-4 • Transient Elastography • CAP	The endpoints and outcomes are not clearly defined in the study. The number of specialist visits that would be saved by the proposed pathway is listed a key readout but there is no clear outcomes in the results section. This is a Canadian based study.	As the level of UK based clinical evidence is important, we decided to not include this study.
Kwok et al (25)	Prospective cohort study Intervention • Blood test • LFTs • Transient Elastography • CAP • Liver Biopsy	Referrals are a mix of hospital and primary care clinics. FibroScan was performed in the course of the diabetic complication assessment visit only. There is no clear patient pathway described in the study This is a Hong-Kong based study	As the level of UK based clinical evidence is important, we decided to not include this study as well.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Please find below the PRISMA flow diagram



Structured abstracts for unpublished studies

We do not provide any unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Search strategy for adverse events

Date search conducted:	August, 10 2021
Date span of search:	From 2003 to today
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
As no adverse events were reported since 2003 (date of first CE mark), this section was not filled.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Not applicable	
Inclusion and exclusion criteria:	
Not applicable	
Data abstraction strategy:	
Not applicable	

Adverse events evidence

Not applicable.

Study	Design and intervention(s)	Details of adverse events	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Not applicable

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT562 FibroScan for assessing liver fibrosis and cirrhosis in primary care

Company evidence submission

Part 2: Economic evidence

Company name	Echosens SA
Submission date	October, 19th 2021
Contains confidential information	Yes

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		15
Number of studies identified as being relevant to the decision problem.		4
Of the relevant studies identified:	Number of published studies.	4
	Number of abstracts.	0
	Number of ongoing studies.	0

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant studies (published and unpublished)

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
PubMed	Serra-Burriel, 2019, Spain (1)	The final cohort includes 6,295 patients from six different countries: France (FR), Spain (ES), Denmark (DK), United Kingdom (UK), Germany (DE), and Hong Kong (HK). The cohorts from ES, DE and HK include patients from the general population above 18 years, the cohort from France includes patients from the general population above 45 years, the cohort from UK includes patients above 18 years with risk factors for chronic liver disease (with hazardous alcohol use or	This economic model compares two different pathways of detection and risk stratification for advanced chronic liver disease (significant fibrosis) in adults with suspicion of NAFLD or ALD in a primary care setting. One pathway uses TE and the other pathway uses aminotransferase activities (as standard of care) to detect patients with chronic liver disease	The perspective of the economic model was generated with provider-direct costs only, with a 30-year time horizon and a 3% discount rate both on health outcomes and costs in 2017 Euros. Health outcomes were measured as QALYs.	Out of the 6,295 patients, 6,199 had successful LSM performed with FibroScan© devices (1.5% failure rate) and were included in the subsequent analysis. The majority of LSM were performed with an M probe (92.3%), whereas the others were performed with an XL probe (7.7%). Mean LSM was 5.6 kPa (±5.0). Among the 6 cohorts, 25 biopsies were performed in the UK cohort out of 98 with LSM >8.2 kPa, with a fibrosis distribution of 32% F0, 24% F1, 12% F2, 24% F3, and 8% F4. According to the developed predictive model, a total of 3.9% (n=238) patients of the general population samples were predicted to have ≥F2 fibrosis, whereas 28.8% (n=157) of at-risk patients were predicted to have developed at least fibrosis stage F2. The mean ICER of the risk-stratification strategy with TE ranged from 2,570 €/QALY (95% CI 2,456 – 2,683) in Spain for a population at-risk for	Sensitivity Analysis To be able to apply the model to different healthcare systems, several assumptions had to be made, mostly regarding care and cost structure, rate of fibrosis progression and treatment effectiveness in different fibrosis stages. Hence, probabilistic sensitivity analysis was performed for these parameters to account for the level of uncertainty associated with the estimates. The results of the present study demonstrate that

		diabetes) and the cohort from Denmark comprised only patients above 18 years at risk for hazardous alcohol consumption.			alcoholic liver disease (age ≥ 45 years) to 6,217 €/QALY (95% CI 5,832€ – 6,601€) in the Hong Kong general population setting.	non-invasive screening for liver fibrosis with transient elastography among the general population, and among patients with risk factors for chronic liver disease, is cost-effective. Conclusion Irrespective of the targeted population, screening for liver fibrosis with optimized algorithms is a highly cost-effective public health intervention, with an average probability of 12% of being cost-saving.
PubMed	Srivastava, 2019, UK (2)	The model piloted competing primary care risk stratification diagnostic strategies for 1000	The authors modelled the standard care in the UK National Health Service (NHS) (scenario 1).	A healthcare payer perspective was adopted. Costs were derived from published	The primary outcome measure was cost per case of advanced fibrosis detected - a surrogate for cost utility. Secondary outcomes included unnecessary referral rates of patients with non-advanced disease, the	Sensitivity Analysis The authors performed a one-way sensitivity analysis on the

		patients with a confirmed diagnosis of NAFLD. The average patient was 50 years old with elevated transaminases.	The use of FIB-4 and ELF in a two-tier stratification approach (scenario 2) was modelled to replicate a local pilot pathway - the Camden and Islington NAFLD pathway. Following an independent evaluation of NILT public health consultants favoured the use of FIB-4 over the NAFLD Fibrosis Score, in part due to a lack of standardization in the diagnosis of diabetes. Fibroscan is increasingly established in secondary care practice, and was incorporated to assess its performance in place of ELF in a two-tier strategy (Scenario 3). One-tier approaches were also considered in which	resources and local costing tariffs (February 2015) for the UK. A 3.5% discount rate was applied. Direct healthcare costs included primary care physicians consultations, blood tests and ultrasound scans.	severity of chronic liver disease complications, liver transplantation and mortality rates. Scenario 1: for 1000 patients with NAFLD over a 1-year timeframe demonstrated 650 patients (65%) were identified as being at low risk of advanced fibrosis and remained in primary care. 8% of false positive rate. Over the 1 year time-horizon, compared to SC these strategies reduced the relative referral rate from primary care to hospital by 70, 67, 56 and 43% for scenarios 2, 3, 4 and 5 respectively; corresponding to 245, 223, 198 and 150 fewer referrals over 1 year per 1000 patients. The number of patients requiring imaging in secondary care reduced by 147, 134, 118 and 60 in scenarios 2, 3, 4 and 5 respectively. These approaches resulted in reductions in referral of patients with non-advanced liver fibrosis (deemed “unnecessary” referrals) by 85, 78, 71 and 42% (absolute reduction) in scenarios 2, 3, 4, and 5 respectively compared to scenario 1;	base-case scenario using a time-frame of 1 year. A clinical effectiveness sensitivity analysis was performed by varying the specificity of standard of care for the detection of advanced fibrosis. The cost benefit was only negated when the specificity of SC for the detection of advanced fibrosis exceeded 0.88, 0.86, 0.80 and 0.68 in scenarios 2, 3, 4 and 5 respectively. Conclusion This study demonstrates that the introduction of non-invasive liver test in primary care has the potential to increase the detection of cases

			SC was supported by ELF (scenario 4), or Fibroscan alone (Scenario 5). Patients identified as being at high-risk of advanced fibrosis were referred to a secondary care specialist. Evaluation included further blood tests, Fibroscan, imaging including US scan (50% of cases, informed by local audit), CT scan (5% of cases, informed by local audit), MRI Liver (5%, informed by local audit) and liver biopsy (15% of cases, informed by local audit).			of NAFLD with advanced fibrosis and cirrhosis, reduce unnecessary referrals to secondary care of patients at low risk of liver disease and to deliver immediate and sustained significant cost savings.
PubMed	Tanajewski, 2017, UK (3)	The study population reflected the patients who were identified in the feasibility study of two primary care	A community-based pathway, which uses transient elastography and hepatologists to stratify patients at	Most unit costs used were derived from NHS reference costs, Personal Social Services Unit and NHS pay scales.	Deterministic cost-effectiveness analysis derived a mean lifetime cost per patient of £9,017 for RSP (risk stratification pathway) and £8,505 for SC (standard of care). The mean QALYs generated was 8.49 for RSP and 8.25 for SC. Incremental cost was	One way sensitivity analyses The two parameters with the highest impact on the ICER were

		practices in Rushcliffe, Nottingham (10 479 adult patients). Within this population, the overall type 2 diabetes prevalence was 3.7% and obesity prevalence was 14.9% of those with recorded BMI measures.	risk of NAFLD, has been implemented and demonstrated to be feasible (NCT02037867) and compared with standard of care. Earlier identification could mean earlier treatments, referral to specialist and enrolment into surveillance programmes.	Where a cost could not be identified, a literature search was conducted or local finance departments were contacted. All costs were inflated to the 2013/2014 financial year.	£512 and incremental QALY was 0.24, providing an ICER of £2,138 per extra QALY gained for RSP compared with SC	(1) altering the rate of fibrosis progression, resulting in an ICER ranging from £928 to £7,032 per QALY, (2) altering the effect of treatment on the rate of progression between NMD (no/mild disease) to SLD (significant liver disease), and SLD to CC from the largest to no reduction 2), resulting in an ICER ranging from −£1,895 to £5,969 per QALY. Multiway sensitivity analyses When it was assumed that detecting and treating patients with fibrosis have no effect on disease progression (transition probabilities from

						NMD+ and SLD+ are the same as those from NMD− and SLD−, respectively), the ICER increased to £18,130/QALY. When it was assumed that diagnosing or treating patients with CC has no effect on disease progression and mortality, the ICER increased to £7,669/QALY Conclusion: Implementation of a community-based risk stratification pathway is likely to be cost-effective.
PubMed	Crossan, UK, 2019 (4)	Patient population and setting This was a modelling study that did not include patient data. The model considered a	The study included 3 scenarios with different interventions. Scenario 1: immediate referral of all patients diagnosed with	UK pounds (£)	Mean total cost per person (in £) over a five-year period of three different two tier non-invasive fibrosis testing strategies, at 5% and 15% prevalence of advanced fibrosis.	Sensitivity analysis By increasing the prevalence of advanced fibrosis to 15%, the referral rate increased in scenario 2 to 15.7% (FIB4 plus

		hypothetical cohort of 1,000 unselected patients with NAFLD who are tested for the presence of advanced fibrosis in a primary care setting	NAFLD to secondary care Scenario 2: At primary care level, testing all patients with NAFLD with a NIT (FIB-4 then ELF or FibroScan). If the NIT is suggestive of ≥F3 (advanced fibrosis), refer patients to secondary care for treatment and management. If the NIT score indicates low risk for advanced fibrosis (<F3), treat and manage patient in primary care. Scenario 3: Biopsy all patients; treat and manage all patients with advanced fibrosis at secondary care. Refer those with <F3 for treatment and management in primary care.		<table><tr><th>Test strategy</th><th>Scenario 1 (Refer all)</th><th>Scenario 2 (NIT)</th><th>Scenario 2b (NIT and biopsy)</th><th>Scenario 3 (Biopsy all)</th></tr><tr><td colspan="5">5% prevalence of advanced fibrosis</td></tr><tr><td>FIB4 followed by ELF</td><td>1,033</td><td>894</td><td>759</td><td>1,603</td></tr><tr><td>FIB4 followed by Fibroscan</td><td>1,100</td><td>963</td><td>839</td><td>1,603</td></tr><tr><td>FIB4 followed by Fibrotest</td><td>1,208</td><td>1,074</td><td>947</td><td>1,603</td></tr><tr><td colspan="5">15% prevalence of advanced fibrosis</td></tr><tr><td>FIB4 followed by ELF</td><td>1,378</td><td>1,248</td><td>1,350</td><td>2,147</td></tr><tr><td>FIB4 followed by Fibroscan</td><td>1,444</td><td>1,318</td><td>1,304</td><td>2,147</td></tr><tr><td>FIB4 followed by Fibrotest</td><td>1,579</td><td>1,456</td><td>1,408</td><td>2,147</td></tr></table> Sequential use of NITs provided lower secondary care referral rates and greater cost savings compared to other scenarios over 5 years, with 90% of patients managed in primary care and cost savings of over 40%.	ELF), 17.1% (FIB4 plus Fibroscan) and 19.7% (FIB4 plus Fibrotest). By using NAFLD fibrosis score as first tier testing instead of FIB4, the referral rate in scenario 2 increased by 0.6-2.4% depending on the second-tier test used Conclusion: The sequential use of NITs in primary care is an effective way to rationalize secondary care referrals and is associated with significant cost savings.

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Transient elastography for screening of liver fibrosis: cost-effectiveness analysis from six prospective cohorts in Europe and Asia. Serra-Burriel, 2019. (1)	
What are main differences in resource use and clinical outcomes between the technologies?	With liver stiffness measurement lower than 9.5 kPa the probability of fibrosis stage ≥F2 was 9.7% only, while higher than 9.5 kPa the probability increased to 52.4% for this at-risk population. The distribution of fibrosis staging in the general population (ES and FR cohorts), risk population for both NAFLD/ALD (UK cohort) and risk population for ALD (DK cohort) differs significantly (p<0.001). The other two serum surrogate fibrosis markers had the following 3-class accuracies: FIB-4 59.4% (95% CI 57.1 – 61.5%) and NFS 55.5% (95% CI 53.3 – 57.6%)
How are the findings relevant to the decision problem?	The authors aimed to explore the cost-effectiveness of transient elastography (TE) as a screening method to detect liver fibrosis in a primary care pathway.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Model shows that screening program for the detection of liver fibrosis with transient elastography at primary care centres is a highly cost-effective intervention and potentially cost-saving and could represent a valuable public health strategy in the era of NAFLD epidemics. FibroScan can enable a test to be done non-invasively and delivery of care in primary care setting
Will any information from this study be used in the economic model?	Not likely as the model is a cost consequence model.
What cost analysis was done in the study? Please explain the results.	It was a cost-effectiveness analysis using real-life individual patient data from 6 independent prospective cohorts. TE with the proposed cut-offs outperformed fibrosis scores in terms of accuracy. Screening with TE was cost effective with mean incremental cost-effectiveness ratios ranging from 2,570 €/QALY (95% CI 2,456 - 2,683) for a population at-risk for

	alcoholic liver disease (age ≥45 years) to 6,217 €/QALY (95% CI 5,832 - 6,601) in the general population. Overall, there was a 12% chance of TE screening being cost-saving across countries and populations.
What are the limitations of this evidence?	Only 5.5% of patients included in the analysis underwent liver biopsy. The economic model had several assumptions, mostly regarding care and cost structure, fibrosis progression rate and treatment effectiveness. And it has been proposed that serum biomarkers should be used as a first step for liver fibrosis detection in the general population, leaving TE for a second step
How was the study funded?	Grant support: EIT Health project 2018, project number EIT 18258; BMBF Liver Systems Medicine, project number LiSyM 031L005; The Danish study was funded by Innovation Fund Denmark, the European Union's Horizon 2020 Research and Innovation Program (grant agreement number 668031). This study was funded by a grant awarded to PG (PI16/00043), integrated in the Plan Nacional I+D+I and cofounded by ISCIII-Subdirección General de Evaluación and European Regional Development Fund FEDER.

Cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for non-alcoholic fatty liver disease. Srivastava, 2019. (2)	
What are main differences in resource use and clinical outcomes between the technologies?	The impact of introducing non-invasive tests into primary care using FIB-4 and ELF (Scenario 2), FIB-4 and TE (Scenario 3), ELF alone (scenario 4) or TE alone (Scenario 5) was assessed. Over the 1 year time-horizon, compared to SC these strategies reduced the relative referral rate from primary care to hospital by 70, 67, 56 and 43% for scenarios 2, 3, 4 and 5 respectively; corresponding to 245, 223, 198 and 150 fewer referrals over 1 year per 1000 patients. This reduced the need for investigation performed in secondary care. The number of patients requiring imaging in secondary care reduced by 147, 134, 118 and 60 in scenarios 2, 3, 4, and 5 respectively, whilst 25, 22, 20 and 10 fewer patients required endoscopy after 1 year per 1000 patients referred.

	The requirement for liver biopsy was reduced by 37, 33, 30 and 15 patients in scenarios 2, 3, 4 and 5 respectively. These approaches resulted in reductions in referral of patients with non-advanced liver fibrosis (deemed "unnecessary" referrals) by 85, 78, 71 and 42% (absolute reduction) in scenarios 2, 3, 4, and 5 respectively compared to scenario 1; corresponding to 275, 253, 231 and 137 reduction in inappropriate referrals from 324 patients in scenario 1 over the 1-year time horizon. Considering cirrhosis specifically, over the 1-year timeframe, employing each of the strategies improved detection by 1 patient per 1000 population compared to the SC. Specifically, an extra 1.2 (113%), 1.2 (116%), 1.3 (128%) and 1.4 (136%) cirrhotic patients per 1000 population were detected in scenarios 2, 3, 4 and 5 respectively over 1 year compared to SC.
How are the findings relevant to the decision problem?	All of the scenarios using non-invasive liver tests in primary care permitted the earlier identification of advanced fibrosis/ cirrhosis, creating opportunities to modify fibrosis progression. A modest reduction in hospital admissions for other complications of chronic liver diseases including jaundice, ascites and hepatic encephalopathy was demonstrated.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Of interest to commissioners, the implementation of non-invasive liver test (NILT) in primary care offers the potential to reduce the total number of referrals, and in particular the unnecessary referral of patients who have minimal fibrosis. Over a 1-year horizon, there was a reduction in total referrals of 70, 63, 56 and 29% in scenarios 2, 3, 4 and 5 respectively, with an 85, 78, 71 and 42% reduction in referrals of patients with non-advanced disease. Utilizing Fibroscan alone was most effective in detecting patients with advanced fibrosis, whilst employing FIB-4 and ELF delivered the greatest cost saving. It supports the claim that FibroScan in primary care could reduce unnecessary referrals to specialist or secondary care, enables a test to be done non-invasively in primary care setting and enables earlier accurate diagnosis

Will any information from this study be used in the economic model?	Not likely as the model is a cost consequence model.
What cost analysis was done in the study? Please explain the results.	It was a cost-saving study. The requirement for liver biopsy was reduced by 37, 33, 30 and 15 patients in scenarios 2, 3, 4 and 5 respectively. This translated into cost savings in secondary care investigation in the first year per 1000 patients referred of £165,530.04, £150,184.67, £133,505.60 and £68,256.85 for scenarios 2, 3, 4 and 5 respectively. Compared to standard of care (scenario 1) which cost £670,504 over 1 year, the incremental reductions in healthcare spending achieved through use of NILT in each scenario were £169 K, £152 K, 101 K and 27 K per 1000 patients in 1 year in scenarios 2, 3, 4 and 5 respectively equating to reductions of 25, 23, 15 and 4%. Using cost-per-case of advanced fibrosis as a surrogate for cost utility, all scenarios were favourable to SC (£25,543.02), with the model predicting cost-per-case of advanced fibrosis at £8,932.19, £9,083.78, £9,487.26 and £10,351.67 in scenarios 2, 3, 4 and 5 respectively over the 1 year timeframe. From a commissioning perspective, a significant contributor to the immediate cost saving was the reduction in secondary care referrals. Compared to scenario 1 (£41,300 per 1000 patients over 1 year), cost-savings attributable to reduced specialist referral were £28,895, £26,216, £23,305 and £11,915 in scenarios 2, 3, 4 and 5 respectively, equating to 70, 63, 56 and 29% reductions.
What are the limitations of this evidence?	The model was populated with the best available published evidence. A lack of high quality data for some variables was remedied with expert opinion. The model assumes that use of ELF and Fibroscan as second-tier tests has the same performance characteristics as a first-tier test. This may under-estimate the performance of the pathway. The model was limited to FIB-4, ELF and Fibroscan and examines fibrosis, but not NASH, and so may underestimate disease progression. The base case scenario could miss cases of NAFLD with advanced fibrosis but normal liver function tests.

How was the study funded?	This work was supported by an unrestricted grant from Siemens Healthineers.
Economic evaluation of a community based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study. Tanajewski, 2017 (3)	
What are main differences in resource use and clinical outcomes between the technologies?	No clinical outcomes available
How are the findings relevant to the decision problem?	A major challenge with chronic liver injury is the absence of symptoms until decompensation occurs, which is associated with a high mortality and increased healthcare utilisation. Thus, if the burden of liver disease is to be reduced, it can only be achieved via the reduction in aetiological exposures (which are rising not falling), or by targeting the asymptomatic via screening or case-finding strategies. The ability to intervene earlier in the natural history of liver disease depends on the idea that hepatic fibrosis is reversible or can at least have its progression retarded by intervention.
Does this evidence support any of the claimed benefits for the technology? If so, which?	This study showed that implementation of risk stratification pathway (RSP) in the community is likely to be cost-effective according to UK cost-per-QALY thresholds, even in the presence of significant uncertainty around estimates. It supports the claim that FibroScan enables a test to be done non-invasively in primary care setting
Will any information from this study be used in the economic model?	Not likely as the model is a cost consequence model.
What cost analysis was done in the study? Please explain the results.	It was a cost-effectiveness analysis. In the probabilistic cost-effectiveness analysis, the mean lifetime cost per patient (2.5% and 97.5% percentiles) was £10,307 (£3,811 and £20,442) and £10,082 (£3,494 and £20,793) for RSP and SC, respectively. The mean QALYs generated per patient (2.5% and 97.5% percentiles) were 7.93 (2.80 and 11.09) for RSP and 7.72 (2.78 and 10.67) for SC. Incremental cost and QALYs were £225 (−2699 and 2856) and 0.21 (−0.1 and 0.65), respectively. The ICER (2.5% and 97.5% percentiles) was −£1,010 (−£40,583 and £50,023). There was a 37% probability that RSP dominated SC and 85% probability that RSP was cost-effective at the UK willingness-to-pay threshold of £20,000/QALY

What are the limitations of this evidence?	Limitations of our model are primarily due to the lack of appropriate data available. Data on fibrosis progression are limited to paired biopsy studies of secondary care patients, which may not reflect the population within the model who are asymptomatic and have been specifically identified due to an underlying risk factor. The sensitivity and specificity of transient elastography within a primary care setting are currently unknown, as there are practical and ethical aspects of performing liver biopsies in a community setting; this represents a limitation.
How was the study funded?	This work was funded by the East Midlands Academic Health Science Network (EMAHSN) and the University of Nottingham.

Referral pathways for patients with NAFLD based on non-invasive fibrosis tests: diagnostic accuracy and cost analysis. Crossan et al. 2019 (4)	
What are main differences in resource use and clinical outcomes between the technologies?	This was a modelling study that did not include patient data.
How are the findings relevant to the decision problem?	The findings support a two-tier approach, with FIB-4 as the initial triaging test, followed by ELF, Fibroscan or Fibrotest in patients with an indeterminate FIB-4. This would result in a referral rate of approximately 10% and cost savings of at least 40% compared to a “refer all” strategy. Therefore, a simple triaging algorithm is key in order to accurately select patients who need further investigation,
Does this evidence support any of the claimed benefits for the technology? If so, which?	The authors therefore modelled a pathway using non-invasive fibrosis tests in primary care to triage patients for secondary care referrals based on diagnostic accuracy and decision curve analysis. This evidence supports that FibroScan can enable a procedure to be done non-invasively, in primary care setting and reduce unnecessary referrals to secondary care.
Will any information from this study be used in the economic model?	Not likely as the model is a cost consequence model.
What cost analysis was done in the study? Please explain the results.	It was a cost-saving study. Modelling of this pathway resulted in reducing the burden of unnecessary referrals by 90%, reducing cost per patient by 40% and accurately selecting those patients at greatest risk of advanced fibrosis and disease progression.

What are the limitations of this evidence?	This was a modelling study that did not include patient data. The authors opted to use a rudimentary cost analysis rather than Markov modelling as there is too much uncertainty in the assumptions for the latter, due to the lack of relevant long term data about the natural history and treatment. Moreover, the lack of any approved therapy for NAFLD at the moment also makes this approach less relevant from a therapeutic point of view. ELF score is not liver specific and might lead to false positive results when other fibrotic conditions, such as pulmonary fibrosis or chronic kidney disease, are present. Fibroscan might also lead to false positive results in patients with heart failure.
How was the study funded?	The study was part of a larger project funded by UK NIHR Health Technology Assessment Program that determined the cost-effectiveness of NITs in patients with viral hepatitis (B and C), alcoholic liver disease and NAFLD

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

People having a FibroScan to assess for liver fibrosis or cirrhosis (as per current NHS practice). The patient group comprises people with non-alcoholic fatty liver disease, suspected non-alcoholic fatty liver disease (for example, people with metabolic syndrome or type-2 diabetes), alcohol-related liver disease, suspected alcohol-related liver disease (for example, based on hazardous alcohol use), or hepatitis.

The model has the flexibility to analyse the following subgroups separately too:

- People with non-alcoholic fatty liver disease;
- People with alcohol-related liver disease;
- People with hepatitis infection.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

The intervention being assessed is FibroScan done outside secondary or specialist care (for example, GP or community services). The comparator being assessed is FibroScan done in secondary or specialist care. There was no deviation from the scope in determining the comparator.

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

A decision tree approach was selected to describe the potential patient pathways. This model is initiated at the point from which an individual is identified as requiring FibroScan. This coincides with the diagram in Part 1, Section 3, after the FIB-4 has been calculated and the patient pathway indicates intermediate to high risk and a need for assessment of liver stiffness by transient elastography.

The decision tree structure allows the comparison of performing this transient elastography outside secondary care compared to within secondary care by breaking down the process into binary decisions.

In both treatment arms the patient first may decide to attend or not attend the scheduled scan. If the patient does not attend the scan, then for patients with underlying liver disease, the diagnosis will be missed and the liver disease will remain untreated. If the patient attends the scan, then for a small proportion of patients the scan may fail to produce results. In these cases, similarly to those not attending the scan, the diagnosis will be missed and the liver disease will remain untreated for the proportion of patients with underlying liver disease. When the scan produces a results, depending on the severity of the liver fibrosis, the patient may require specialist treatment, or they may only require a behavioural intervention or no intervention at all.

In the treatment arm assessing FibroScan outside of secondary or specialist care, patient requiring specialist treatment are assumed to be referred to a hepatologist, while in secondary or specialist care, patients are assumed to be invited for a follow-up visit to initiate specialist treatment.

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification
Once patient has attended scan, the proportion requiring referral to a hepatologist is the same regardless of whether the scan is received inside or outside of secondary care	The underlying prevalence of liver disease is not affected by the care setting. Furthermore, the ability of the scan to identify liver disease is the same regardless of care setting
Once patient has attended scan, the failure rate of the scan in returning an image is the same, regardless of whether the scan is received inside or outside of secondary care	The likelihood that the scan fails to return a liver stiffness measurement is dependent on the patient characteristics, and not the care setting.
In the current submission, the likelihood of a patient attending the scan is assumed to be the same across all subgroups.	Patient behaviour is not expected to differ by subgroup. However, further analyses of the Southampton CCG pilot study may provide subgroup-specific information on attendance rates in the near future.
If the patient does not require a referral to a hepatologist, the likelihood of requiring a behavioural intervention is the same inside or outside of secondary care	Treatment received when a scan shows no requirement for a hepatologist referral is the same regardless of care setting
The proportion of patients requiring referral for specialist treatment within those who have liver disease is assumed to be the same in the subgroups as in the overall population	Data on referrals was available for the overall population from the Southampton CCG pilot study, however, subgroup-specific information was not. The underlying prevalence of liver disease does differ between subgroups, but the distribution of severities at the time of identification was assumed to be the same.
In secondary or specialist care, patients identified as requiring specialist treatment are assumed to be invited for a follow-up visit to initiate the treatment.	In line with UK clinical practice

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution*	How are these values used in the model?
Probabilities for Fibroscan outside of secondary or specialist care				
Attends scan	Southampton CCG	89%	N/A	Residual calculation - Determining proportion attending the scan outside of secondary or specialist care
Does not attend scan	Southampton CCG	11%	Beta (66,533) Range 9% - 14%	Determining proportion failing to attend the scheduled scan outside of secondary or specialist care
Scan Fails	Mean based on clinical studies from the clinical evidence section (5–10)	5%	N/A	Residual calculation - Determining proportion of failed scans outside of secondary or specialist care
Scan produces result	Assumption based on Scan Fails ratio	95%	Beta (4.05, 0.21) Range 65% - 100%	Determining proportion of failed scans outside of secondary or specialist care
Misses diagnosis of liver disease	El Gohary	45%	N/A	Residual calculation - Determining proportion of who have an undetected liver disease
No liver disease	El Gohary	55%	Beta (505,405) Range 52%-59%	Determining proportion of failed scans outside of secondary or specialist care
Requires referral to hepatologist	Southampton CCG	23.6%	Beta (126,407) Range 20% - 27%	Determining proportion of patients requiring specialist treatment
Does not require referral to hepatologist	Southampton CCG	76%	N/A	Residual calculation - Determining proportion not needing specialist treatment
Behavioural intervention	Assumption	100%	Range 90%-100%	Determining proportion of patients requiring behavioural intervention only
No behavioural intervention	Assumption	0%	N/A	Residual calculation - Determining proportion not needing any intervention
Probabilities for Fibroscan in secondary or specialist careText				

Attends scan	Southampton CCG	80%	N/A	Residual calculation - Determining proportion attending the scan in secondary or specialist care
Does not attend scan	Southampton CCG	20%	Beta (79.8,319.2) Range: 16% - 24%	Determining proportion failing to attend the scheduled scan in secondary or specialist care
All other probabilities	Assumption	Same as outside of secondary or specialist care		

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

No extrapolation is used in the model.

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	< 1 year	Any difference between the arms in the model can be captured during the time the scans are performed and follow-up treatments are decided.	Text

Discount rate	None	Due to the short time horizon, no discounting was necessary	Text
Perspective (NHS/PSS)	NHS and PSS included	NICE guidelines	Text
Cycle length	Not applicable	Text	Text
Chance node probabilities	Probabilities for decision tree included in Table 3	Text	Text
Health states	Nodes included in decision tree model are as follows: Decision Node: FibroScan in secondary care or outside secondary care. Chance nodes: Attends the scan, Scan fails, Liver disease without scan or with failed scan; Referral to hepatologist needed; Behavioural intervention needed Terminal nodes: Behavioural intervention, No behavioural intervention, Requires referral to hepatologist, Misses diagnosis of liver disease, No liver disease	Captures patient pathway from identification for need of a scan to the time point where treatment decisions are made.	Text
Sources of unit costs	NHS Reference Costs 2019-20 PSSRU Unit costs of health and social care 2020	NICE guidelines	https://www.england.nhs.uk/national-cost-collection/#ncc1819 https://www.pssru.ac.uk/project-pages/unit-costs/

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

The model structure chosen is a decision tree, therefore no transition matrix was needed. Decision tree chance node probabilities were described in Table 3 above. No transformation was done, the model relies of proportions of patients as observed in the data sources.

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

Capital equipment range of products (excluding VAT):
FibroScan 430 Mini+ with M probe: £45,000
FibroScan 530 Compact with M probe: £45,000
FibroScan 630 Expert with M probe: £70,000
S or XL Probe: £16,250
CAP/"SmartExam": £18,000

FibroScan "Go" (230) – Pay Per Exam – excluding VAT
Minimum contract term is 36 months with a minimum contract value (minimum 25 exams per month, actual exams will be invoiced when over 25 exams).
Customer pay £58 per patient exam completed (10 valid measurements).
Contract includes all training, installation, service and calibration costs, hardware (box), both probes M and XL and CAP/"SmartExam".

If the list price is not used in the model, provide the price used and a justification for the difference.

The list prices provided above only incorporate purchase price of the scanners only. Before use, one session (half a day) of training will be required for the staff operating the scanners. Furthermore, each scanner may be reused to scan patients a large number of times over its lifetime. Therefore, the model relies on a cost per scan instead of the list price of the scanners themselves.

FibroScan outside secondary or specialist care will be provided at the price of £70 per scan. This price includes the purchase price of the machines, training costs as well as maintenance costs over the lifetime of the device.

Fibroscan is already used in secondary or specialist care, here it was modelled using the cost of ultrasound elastography (£43.93; Code: RD48Z; NHS Reference Costs 2019-20).

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

Unit costs in the model

Resource	Unit cost	Source	Code
Cost of scan in secondary or specialist care	£43.93	National Schedule of NHS costs 2019-20;	IMAGOP RD48Z; Ultrasound Elastography
Staff time to perform and evaluate scan in secondary or specialist care	£93.19	National Schedule of NHS costs 2019-20	306 Hepatology WF01B; Non-Admitted Face-to-Face Attendance, First (Non-Consultant led)
Staff time to perform and evaluate scan outside of secondary or specialist care	£42.00 / hour	PSSRU Unit Costs of Health and Social Care 2020	Nurse (GP practice) incl. qualification costs
Referral to hepatologist from outside of secondary or specialist care	£207.86	National Schedule of NHS costs 2019-20	306 Hepatology WF01B; Non-Admitted Face-to-Face Attendance, First (Consultant led)
Follow-up visit to hepatologist after scan in secondary or specialist care	£164.75	National Schedule of NHS costs 2019-20	306 Hepatology WF01A; Non-Admitted Face-to-Face Attendance, Follow-up (Consultant led)
General practitioner consultation	£39.23	PSSRU Unit Costs of Health and Social Care 2020	General practitioner per patient contact lasting 9.22 minutes incl. qualification costs

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

Resource use was modelled based on the patient pathways in the Southampton CCG pilot study

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

Implementing the FibroScan pathway outside of secondary or specialist care requires the following resources:

- FibroScan machine
- Trained nurse to carry out the scan with FibroScan and provide assessment of the results followed by a tailored conversation appropriate to the results (e.g. referral to specialist care or to the general practitioner, if needed)
- General practitioner (GP) to provide behavioural interventions (if necessary signposting to support services, advise on behaviour change, lifestyle choices, alcohol consumption, weight management, exercise programmes, vaccinations, etc.).

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

Patient outcomes are not expected to change by shifting the use of Fibroscan to outside of secondary or specialist care. Patients identified as needing specialist treatment will still be referred to a hepatologist, while those not requiring specialist treatment will still be advised on behavioural changes by the general practitioner (GP). Use of FibroScan outside of secondary or specialist care is expected to reduce the overall number of visits to hepatology departments and unnecessary referrals, therefore freeing up resources for the NHS.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

GP nurses using FibroScan will need to be trained in using the equipment and evaluation of the scan results. This training will be undertaken by Echosens. Training costs as well as maintenance costs are included in the per scan price of Fibroscan.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

	FibroScan outside of secondary or specialist care	Fibroscan in secondary of specialist care	Difference in resource use costs (technology vs comparator)
Cost of scans performed including staff time for consultation	£80.5	£137.12	-£56.62
Cost of hepatologist referrals / visit	£207.86	£164.75	£43.11
Cost of behavioural interventions	£39.23	£39.23	£0.00
Cost of missed appointments (staff costs)	£10.50	£93.19	-£82.69

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

No adverse events were included as use of FibroScan was not associated with any adverse events in its clinical trial programme or during its use in secondary or specialist care.

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Adverse event	Items	Cost	Source
Adverse event 1	Technology	Text	Text
	Staff	Text	Text

	Hospital costs	Text	Text
	[Other items]	Text	Text
	Total	Text	Text
Adverse event 2	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	Text	Text
	[Other items]	Text	Text
	Total	Text	Text
[Add more rows as needed]			

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

No additional costs were included in the evaluation

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

Due to increased attendance rates with the use of FibroScan outside of secondary or specialist care, it is hypothesised that liver disease may be identified earlier in patients who would have not attended the scan is a secondary care setting. Therefore, lifetime costs for these patients are likely to be reduced as cost of treatment of earlier phases of liver disease is lower than cost of treatment of later stages (see e.g. Crossan et al., 2015) (11)

Furthermore, the model includes the cost of a GP nurse (band 4 or higher) to perform and evaluate the scans outside of secondary or specialist care. However, in the Southampton CCG pilot study, over time the responsibility of scanning and evaluation was shifted to a trained health care assistant (band 2) to further reduce operational costs.

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.

- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost	Source
Cost per scan/patient	£70 per scan	Echosens
Staff time for scan and evaluation / scan / patient	£10.50	PSSRU Unit costs 2020, 15 minutes
Total cost / scan / patient	£80.50	

Table 8 Total costs for the comparator in the model

Description	Cost	Source
Cost per scan/patient	£43.93	National Schedule of NHS costs 2019-20;
Staff time for scan and evaluation / scan / patient	£93.19	National Schedule of NHS costs 2019-20;
Total cost / scan / patient	£137.12	

Results

Table 9 Base-case results

Results of the economic evaluation confirmed findings by observational studies described in Section 1 of this submission. Due to the increased attendance rates at scans, the use of FibroScan outside of secondary or specialist care identifies more patients with liver disease requiring some form of intervention (specialist treatment by hepatologist or a behavioural intervention by a GP). Despite the increase of cases identified, FibroScan used outside of secondary or specialist care reduces costs by reducing the number of visits to hepatologist departments as well as reducing the opportunity costs of missed scan appointments.

	Mean discounted cost per patient per scan using FibroScan outside of secondary or specialist care (£)	**Mean discounted cost per patient per scan using FibroScan in secondary or specialist care (£)**	**Difference in mean discounted cost per patient (£): technology vs comparator 1***
Scan costs	£71.63	£109.70	-£38.06
Missed appointment costs	£1.16	£18.64	-£17.48
Hepatologist referral costs	£41.54	£29.60	£11.94
Behavioural intervention costs	£25.32	£22.77	£2.56
Total cost	**£139.65**	**£180.57**	**-£41.05**
Number of referrals to hepatologist after scan	0.20	0.18	0.02
Number of referrals to behavioural intervention	0.65	0.58	0.07
Missed diagnosis of liver disease	0.07	0.11	-0.04
Total number of visits to hepatology department	0.20	0.94	-0.74

Results for subgroups

	Mean discounted cost per patient per scan using FibroScan outside of secondary or specialist care (£)	Mean discounted cost per patient per scan using FibroScan in secondary or specialist care (£)	Difference in mean discounted cost per patient (£): technology vs comparator 1*
Patients with non-alcoholic fatty liver disease	£139.67	£180.70	-£41.03
Patients with alcohol-related liver disease	£134.86	£177.48	-£42.62
Patients with hepatitis-related liver disease	£173.11	£203.07	-£29.96

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

Not relevant

Describe the differences between the base case and each scenario analysis.

Not relevant

Describe how the scenario analyses were included in the cost analysis.

Not relevant

Describe the evidence that justifies including any scenario analyses.

Not relevant

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

	Mean discounted cost per patient per scan using FibroScan outside of secondary or specialist care (£)	**Mean discounted cost per patient per scan using FibroScan in secondary or specialist care (£)**	**Difference in mean discounted cost per patient (£): technology vs comparator 1***
Patients with non-alcoholic fatty liver disease	£139.67	£180.70	-£41.03
Patients with alcohol-related liver disease	£134.86	£177.48	-£42.62
Patients with hepatitis-related liver disease	£173.11	£203.07	-£29.96

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Parameter uncertainty was assessed in the univariate (one-way) sensitivity analysis and probabilistic sensitivity analysis (PSA).

Univariate deterministic sensitivity analysis was performed where each parameter was varied according to its 95% confidence internal (CI), while holding all other parameters constant. Where the published study or source for parameter values did not report standard errors or CIs, or patient counts which would have allowed calculation of CIs, 10% variation of the mean was assumed. All parameters with uncertainty were included in the sensitivity analyses. Unit costs and resource use for non-drug resources were not independently varied, but as composite pathway costs associated with chance nodes within the model.

PSA was also performed to account for the combined variability in outcomes due to parameter uncertainty. The probabilistic analyses were run for 1,000 replications where parameter estimates were repeatedly sampled from probability distributions to determine an empirical distribution for total costs per scan per patient. For chance node probabilities beta distributions were used as described in Table 3 above, while chance node costs were assumed to follow normal distributions with a 10% standard deviation around the mean.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

All chance node probabilities were included in the sensitivity analyses as these are based on patient counts in individual studies, therefore estimated proportions are subject to parameter uncertainty. Pathway cost (including resource use frequencies and unit costs) were also included to account for the possibility of differences in e.g. number of visits requires or the length of time required to perform the scan for specific patients. Distributions and ranges for parameters not already included in Table 3 above are presented here:

Parameter/outcomes	**Relevant results**	**Range or distribution***
Cost for scan outside of secondary or specialist care	£80.50	Normal (SD 10%) Range: £64.72 - £96.28
Cost of missed appointment outside of secondary or specialist care	£10.50	Normal (SD 10%) Range: £8.44 - £12.56
Cost for scan in secondary or specialist care	£137.12	Normal (SD 10%) Range: £110.24 - £163.99
Cost of missed appointment in secondary or specialist care	£93.19	Normal (SD 10%) Range: £74.92 - £111.45
Cost of hepatologist referral	£207.86	Normal (SD 10%) Range: £167.12 - £248.60
Cost of hepatologist follow-up	£164.75	Normal (SD 10%) Range: £132.46 - £197.04
Cost of GP appointment for behavioural intervention	£39.23	Normal (SD 10%

		Range: £31.54 - £46.92

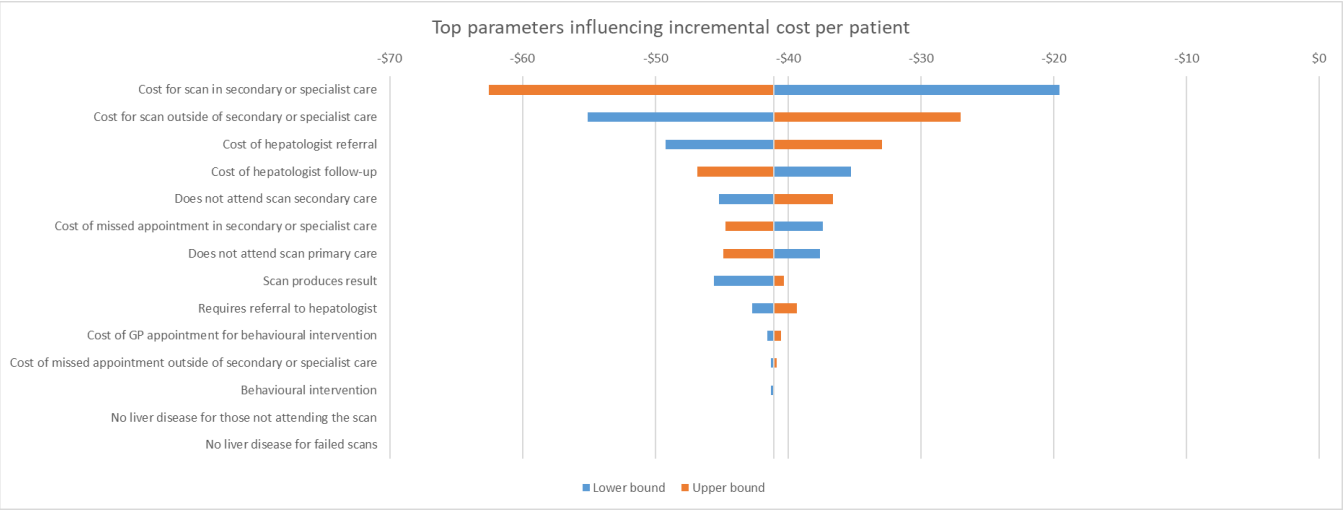
If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

All parameters were included in the sensitivity analyses.

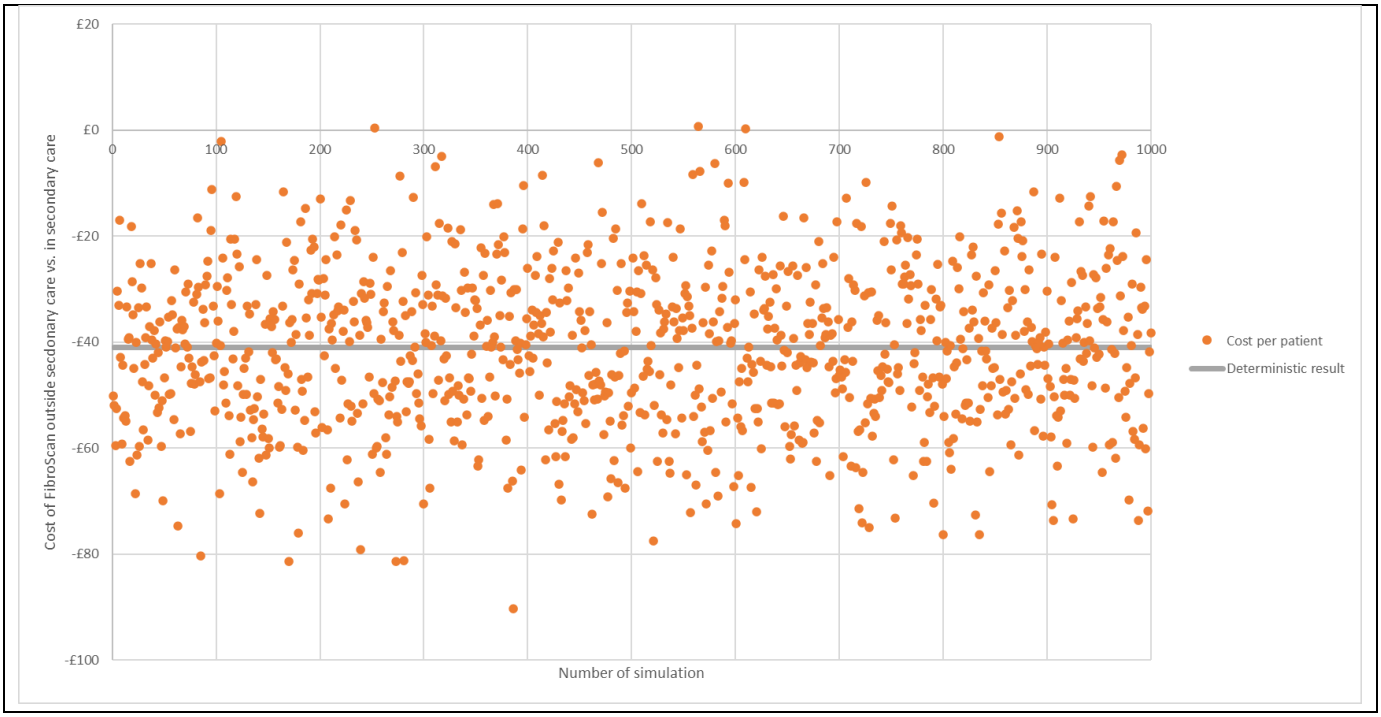
Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

Deterministic Sensitivity Analysis



Probabilistic Sensitivity Analysis



What were the main findings of each of the sensitivity analyses?

The one-way sensitivity analyses showed results to be robust, with all results showing use of Fibroscan outside of secondary or specialist care to be cost saving versus its use in secondary or specialist care. Not surprisingly, the costs of the scans themselves had the highest impact on the incremental cost per scan per patient. Note that the model includes the cost of a band 4 nurse to perform the scans in primary care, whereas in the Southampton CCG pilot study the task was shifted to be performed by a health care assistant, which may increase the cost saving associated with use of Fibroscan outside of secondary and specialist care.

The PSA results also showed that use of Fibroscan outside of secondary or specialist care can be assumed to be cost saving compared to its use in a secondary care setting. Only 0.3% of simulations resulted in FibroScan in primary care not showing cost savings compared to FibroScan in secondary care. The 95% confidence interval for the incremental cost of the use of FibroScan outside of secondary or specialist care versus its use in secondary care was estimated to be -£12.66 to -£71.44 per scan per patient.

What are the main sources of uncertainty about the model's conclusions?

The difference between attendance rates for the scans drives the model. Improved attendance at a primary care setting can be explained by convenience for the patients. There is very little uncertainty around whether use of FibroScan outside of secondary or specialist care is cost saving, however, there is some uncertainty around the exact magnitude of this cost saving as it depends on the level staff which will be used to perform the scans in a primary care setting as well as the exact time needed for the scans (which also influences the cost of missed scan appointments).

Miscellaneous results

Include any other relevant results here.

Not relevant

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

The cost-consequence analyses have undergone both conceptual and technical validation. Conceptual validation was provided by comparison with the pathways described in the Southampton CCG pilot study and consultations with internal Echosens clinical experts with experience of patient referral practiced in the UK.

In addition to conceptual validation, a comprehensive and rigorous quality check was performed once programming was finished. A model validator not involved in the original programming checked the calculation and reference formulas, and an additional team member checked the values of numbers supplied as model inputs.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

[redacted]

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

The economic evidence from the literature review demonstrates that the introduction of non-invasive liver test in primary care has the potential to increase the detection of cases of NAFLD with advanced fibrosis and cirrhosis, reduce unnecessary referrals to secondary care of patients at low risk of liver disease and to deliver immediate and sustained significant cost savings (2,4) or being cost-effective (3).

With the availability of Fibroscan outside the secondary or specialist care, the model shows 20% and 7% increase in the numbers of referrals to hepatologist specialist treatment and behavioural intervention respectively for the management of liver disease, i.e. indicating an increase in the numbers of patients identified with liver disease. The model also shows a 74% reduction in the total number of visits to a hepatology department. The incremental cost per patient of FibroScan outside secondary or specialist care is -£41.05 compared to the standard of using FibroScan in secondary care. This denotes cost savings.

Furthermore, Southampton CCG study reported increase in uptake of the FibroScan examination (a reduction from 21% to 8.6% of patients who failed to attend scans) from phase 1 to phase 2. The increase in uptake indicates increase in early identification and decrease in missed diagnosis of liver diseases. Cost of management of different liver disease stages reported by Crossan C et.al, 2015 shows increase in cost with the increase in severity of disease. For example- cost of management of mild fibrosis (cost in 2012) was £185 compared to the cost of liver transplantation (cost in 2012) which was £64,122. Hence, it can be inferred that in the long run early identification of disease will result in significant cost savings even over and above the savings captured in the current economic model through the reduced number of secondary or specialist care attendance. (9)

Briefly discuss the relevance of the evidence base to the scope.

The evidence base used in the economic model followed the scope throughout. Only long-term morbidity and mortality implications were not captured explicitly in the model due to the complexity in trying to estimate lifelong outcomes and treatment pathways for patients with different stages of liver disease. However, as mentioned above, identification or liver disease at earlier stages due to increased attendance rated can be assumed to lead to further cost savings.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

The results are consistent with the published literature. Previous studies had demonstrated the acceptability of non-invasive tests to patients and increase in the detection of advanced liver disease in the community FibroScan pathway compared with standard care. (Mansour et al. JHEP Reports 2021, Southampton CCG) (5,12). Furthermore, increased rates of diagnosis by FibroScan which would have been missed by standard diagnostic algorithms have been also reported implying the reduction in missed diagnosis (Harman et al. 2015) (7). In addition, effectiveness of nurse led case finding and GP referrals for management of liver disease have also been reported (El Gohary, 2018). (9)

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The analysis is relevant to all patient groups. Scenario analyses for patient subgroups identified in the scope have also been presented above.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

The analysis describes in detail the patient pathways from the time of identification of the need for a FibroScan to the time where treatment decisions are made (either by a hepatologist or by the GP). The analysis also relies on a pilot study testing the use of FibroScan in the Southampton CCG, therefore captures referral rates that represent a UK population.

The model time horizon is short, and some of the longer terms benefits have not been captured in the calculations. However, there is strong evidence to support that earlier diagnosis is likely to lead to further cost savings.

There is currently no subgroup-specific data on attendance rates for the scans nor on the proportion of patients requiring hepatologist referrals. The calculations can be updated when the subgroup-specific information from the Southampton CCG pilot study becomes available.

Detail any further analyses that could be done to improve the reliability of the results.

A study estimating the proportions of patients invited for a scan in secondary care setting but failing to attend could reduce the uncertainty around the magnitude of improvement in attendance rates between primary and secondary care settings.

5 References

Please include all references below using NICE's standard referencing style.

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3. Tanajewski L, Harris R, Harman DJ, Aithal GP, Card TR, Gkountouras G, et al. Economic evaluation of a community-based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study. BMJ Open. 5 juill 2017;7(6):e015659.

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7. Harman DJ, Ryder SD, James MW, Jelpke M, Ottey DS, Wilkes EA, et al. Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography. BMJ Open. 3 mai 2015;5(4):e007516-e007516.

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10. Harris R, Card TR, Delahooke T, Aithal GP, Guha IN. Obesity Is the Most Common Risk Factor for Chronic Liver Disease: Results From a Risk Stratification Pathway Using Transient Elastography. Am J Gastroenterol. nov 2019;114(11):1744-52.

11. Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Papastergiou V, Thalassinos E, et al. Cost-effectiveness of noninvasive liver fibrosis tests for treatment decisions in patients with chronic hepatitis B in the UK: systematic review and economic evaluation. J Viral Hepat. févr 2016;23(2):139-49.

12. Berzigotti A, Tsochatzis E, Boursier J, Castera L, Cazzagon N, Friedrich-Rust M, et al. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update. J Hepatol. juin 2021;S0168827821003986.

13. Hayward KL, McKillen BJ, Horsfall LU, McIvor C, Liew K, Sexton J, et al. Towards collaborative management of nonalcoholic fatty liver disease (TCM-NAFLD): a « real-world » pathway for fibrosis risk assessment in primary care. Intern Med J. 17 juin 2021;

14. Asphaug L, Thiele M, Krag A, Melberg HO. Cost-Effectiveness of Noninvasive Screening for Alcohol-Related Liver Fibrosis. Hepatol Baltim Md. juin 2020;71(6):2093-104.

15. Tapper EB, Hunink MGM, Afdhal NH, Lai M, Sengupta N. Cost-Effectiveness Analysis: Risk Stratification of Nonalcoholic Fatty Liver Disease (NAFLD) by the Primary Care Physician Using the NAFLD Fibrosis Score. PloS One. 2016;11(2):e0147237.

16. Congly SE, Shaheen AA, Swain MG. Modelling the cost effectiveness of non-alcoholic fatty liver disease risk stratification strategies in the community setting. PloS One. 2021;16(5):e0251741.

6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	23/08/2021
Date span of search:	Enter text.

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

There are over 2,500+ published studies on the use of FibroScan including recent reviews on its use in hepatitis C, hepatitis B and liver fibrosis in secondary care (NICE MIB216, 2020). FibroScan in secondary care is supported by the evidence and is widely used in the NHS.

Search Topic		Search quary with filters
		PubMed
1	Technology and condition	("FibroScan"[Tiab] OR "Vibration Controlled Transient Elastography"[Tiab] OR "Transient Elastography"[Tiab]) AND ("liver"[MeSH Terms] OR "liver"[All Fields] OR "liver fibrosis"[tiab] OR "liver cirrhosis"[tiab]) AND (cost*[tiab] OR economic*[tiab]) AND ("2004/01/01"[PDAT] : "3000/12/31"[PDAT])
2	Setting	"primary care*"[tiab]
3	Economic study	cost*[tiab] OR economic*[tiab]

The large majority of the economic evidence was developed within the secondary care setting.

Search Topic		Search quary with filters	Results
		PubMed	PubMed
Clinical Evidence			
1	Technology, condition and economic studies	("FibroScan"[Tiab] OR "Vibration Controlled Transient Elastography"[Tiab] OR "Transient Elastography"[Tiab]) AND ("liver"[MeSH Terms] OR "liver"[All Fields] OR "liver fibrosis"[tiab] OR "liver cirrhosis"[tiab]) AND (cost*[tiab] OR economic*[tiab]) AND ("2004/01/01"[PDAT] : "3000/12/31"[PDAT])	126
1+2	Technology, condition and setting	("FibroScan"[Tiab] OR "Vibration Controlled Transient Elastography"[Tiab] OR "Transient Elastography"[Tiab]) AND ("liver"[MeSH Terms] OR "liver"[All Fields] OR "liver fibrosis"[tiab] OR "liver cirrhosis"[tiab]) AND ("primary care"[tiab]) AND ("2004/01/01"[PDAT] : "3000/12/31"[PDAT])	53
1+2+3	Technology, condition, setting and economic studies	("FibroScan"[Tiab] OR "Vibration Controlled Transient Elastography"[Tiab] OR "Transient Elastography"[Tiab]) AND ("liver"[MeSH Terms] OR "liver"[All Fields] OR "liver fibrosis"[tiab] OR "liver cirrhosis"[tiab]) AND ("primary care"[tiab]) AND (cost*[tiab] OR economic*[tiab]) AND ("2004/01/01"[PDAT] : "3000/12/31"[PDAT])	15

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Enter text.

Inclusion and exclusion criteria:

Inclusion Criteria

- Clinical data related to FibroScan
- Setting is primary care
- Study presenting economic data
- Data related to the intervention, clinical condition, purpose, specific characteristics and features of FibroScan
- Data related to the same within the same site of the body: *non-invasive diagnostic tool for liver disease*
- Data related to the same patient population for which the devices are intended: adult and paediatric patients, on large sample size (at least 100 patients, except for pregnant women, for whom any clinical data identified on this population will be considered whatever the sample size).
- Data involving humans

Exclusion criteria

- Different device
- Different indication
- Methodology (inappropriate number of patients, case reports, final conclusions not available)
- Pre-clinical studies
- No abstract available
- Non peer-reviewed journal
- Technical notes or journal article
- Duplicate of references
- Language other than English

Data abstraction strategy:

We used a data abstraction form that included the following categories: study country, study design, number of patients, aetiologies, care setting, outcomes measured, interventions, results, thresholds for advanced liver fibrosis and valid measure rate.

Appropriate baseline data specific to each clinical indication was also considered.

One author independently performed data abstraction using this form, with results being compared after completion of document review.

Potential disagreements in abstracted elements were settled through involvement of Echosens Chief Medical Officer

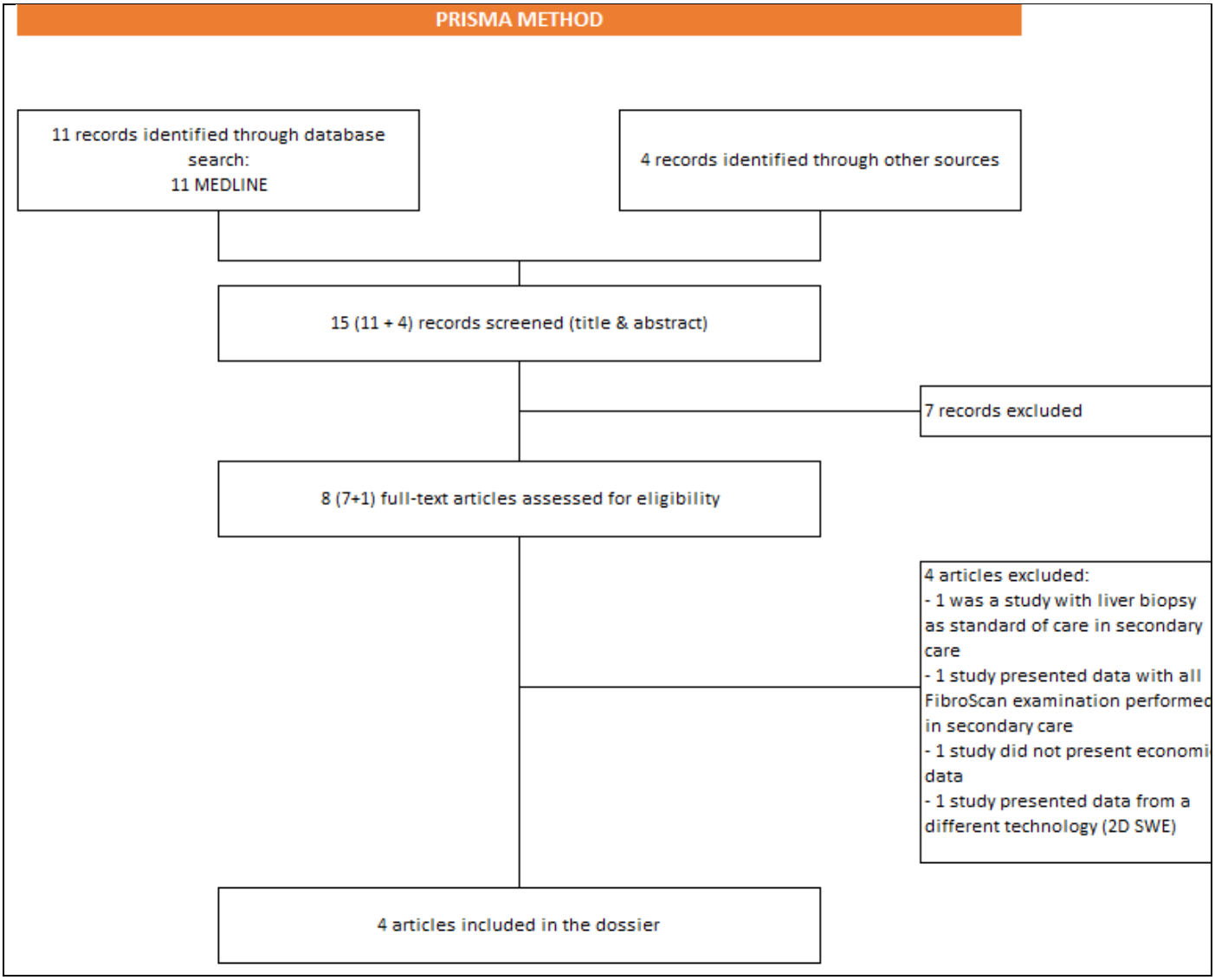
Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Hayward, 2021 (13)	Prospective cohort study Intervention • NAFLD Fibrosis Score (NFS) • FIB-4 • FibroScan	The study suggests that prevalence of clinically significant fibrosis in 'routine' primary care cohort was low. Implementation of the 2-step towards collaborative management-NAFLD fibrosis risk assessment pathway streamlined Hepatology referrals for NAFLD and may facilitate a more cost-effective and targeted use of specialist hepatology resources. However, the study does not present any economic evidence	This study could be considered for the clinical evidence section
Asphaug, 2020 (14)	Cost-effectiveness model. Decision tree with a Markov state-transition model. Intervention: • Liver function test • Ultrasonography • ELF test • Forns Index • FibroScan	The authors used a biopsy-controlled cohort for the short term perspective. The patients were recruited in primary care and secondary care but all the FibroScan procedures were performed within a secondary care setting after referral. The strategies form a spectrum of the likelihood of referral to liver stiffness measurement in hospital-based liver clinics. This is a US study.	No
Tapper, 2016 (15)	Cost-effectiveness in a cohort of 10,000 simulated US patients Intervention • NAFLD fibrosis score • FibroScan • Liver biopsies	The selected standard of care for the comparison was liver biopsy performed in a secondary care setting. This study does not include human subjects and is not based on clinical evidence This is a US study.	A threshold of 15 kPa for a diagnosis of advanced fibrosis is a bit high compared to Echosens interpretation guide and available evidence.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Congly, 2021 (16)	Cost-effectiveness study and budget impact analysis. Intervention: • NAFLD fibrosis score • FIB-4 • Shear Wave Elastography • Transient Elastography	The authors established a community based care pathway using 2D ultrasound shear wave elastography (SWE) to identify high risk patients with NAFLD. FibroScan was also considered in several scenarios of the model. However, FibroScan examinations were performed at a hepatology clinic level, in a secondary care setting. This is a Canada based study	No

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

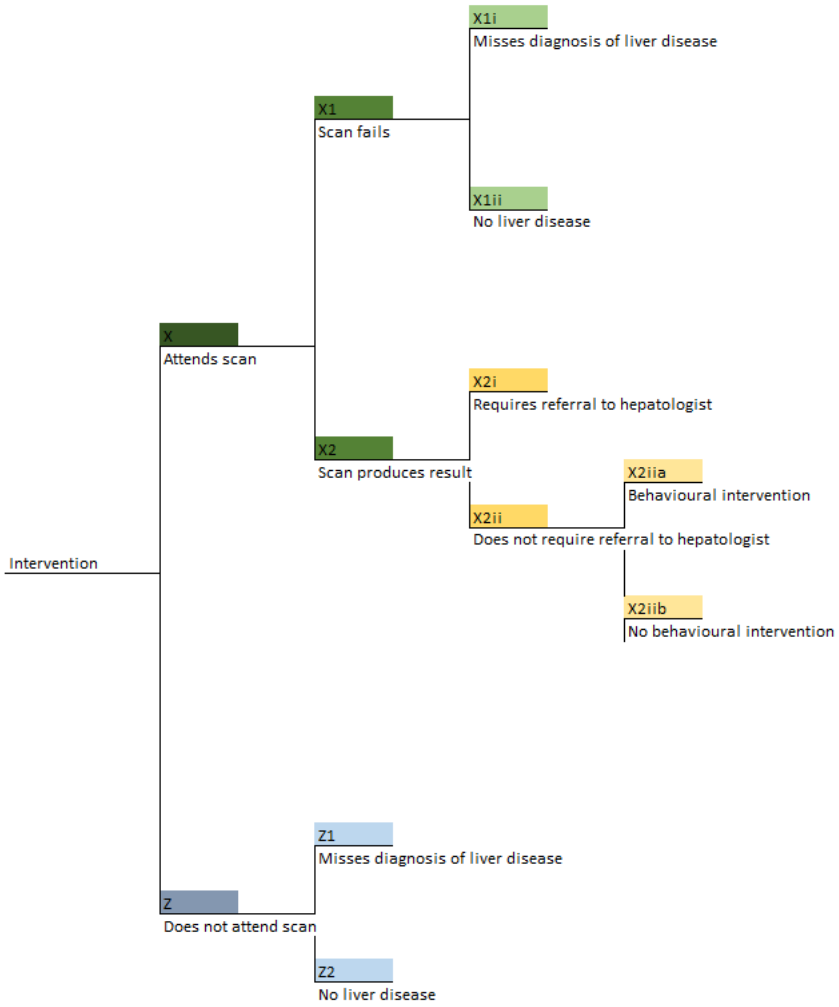


Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission

NICE Medical Technologies Advisory Committee
Title of guidance: FibroScan for assessing liver fibrosis and cirrhosis in primary care [MT562]

Please read the guide to completing a submission fully before completing this template.

Information about your organisation	
Organisation name	British Liver Trust
Contact person's name	Vanessa Hebditch
Role or job title	Director of Communications & Policy
Email	[redacted]
Telephone	[redacted]
Organisation type	Patient/carer organisation (e.g. a registered charity) ☒ Informal self-help group ☐ Unincorporated organisation ☐ Other, please state:
Organisation purpose (tick all that apply)	Advocacy ☒ Education ☒ Campaigning ☒ Service provider ☒ Research ☒ Other, please specify:

What is the membership of your organisation (number and type of members, region that your organisation represents, demographics, etc)?

The British Liver Trust is the UK's leading liver health charity working to improve liver health for all and supporting all adults affected by liver disease or cancer.

We operate throughout the UK and reach over a million people each year. Our website has over 1.5 million unique visitors each year; our online forum has over 28,000 active members, our nurse-led Helpline handles between 400 and 500 enquiries a month, our regular newsletter goes to c17,000 people with liver disease, we run around 250 support groups each year (currently virtual but moving to a mix of virtual and face to face post Covid); we expect to visit around 40 locations per annum with our Love Your Liver Roadshow post Covid, we connect with around 20,000 people via social media.

Please note, all submissions will be published on the NICE website alongside all evidence the committee reviewed. Identifiable information will be redacted.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission

If you haven't already, please register as a stakeholder by completing the stakeholder registration form and returning it to diagnostics@nice.org.uk

Further information about registering as a stakeholder is available on the NICE website.

Did you know NICE meetings are held in public? You can register on the NICE website to attend a meeting up to 20 working days before it takes place. Registration will usually close 10 days before the meeting takes place.

Sources of information

What is the source of the information about patients' and carers' experiences and needs that are presented in this submission?

Information in the submission is collated from a variety of British Liver Trust sources and activities, including:

- Direct feedback and intelligence from patients and carers who contact the British Liver Trust specialist nurse helpline.
- Direct feedback and intelligence from patients and carers who attend British Liver Trust patient support groups
- Outcomes from British Liver Trust public awareness 'Love Your Liver' roadshows, including use of FibroScan as part of these events and associated direct feedback and intelligence from attendees to the roadshow
- Feedback through focus groups of people living with liver disease and those who care for them
- Literature reviews
- Results of patient surveys including a survey of over 2000 people
- Responses through website and social media channels
- Feedback via threads on our online patient forum (over 28,000 members)
- Intelligence from our Patient Advisory Group and Clinical Advisory Group

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission

Impact of the symptoms, condition or disease

1. How do symptoms and/or the condition or disease affect people's lives or experiences?

Liver disease is a silent killer. It affects people when they are relatively young and is a leading cause of death amongst those of working age. It is the second biggest cause of death in those aged between 35-49 years old.

Due to lack of identifiable symptoms, most people with the early stages of fibrosis don't know they have it. Patients who have been diagnoses with fibrosis report confusion about what it means and worry about whether it will progress to cirrhosis.

Patients with cirrhosis often experience pain, debilitating fatigue, jaundice, ascites, variceal bleeds, confusion and brain fog (from hepatic encephalopathy). If the cirrhosis is advanced (decompensated) the prognosis is poor and the only treatment may be liver transplant.

A recent survey of 121 people with advanced liver disease found that when asked about how their condition affects their lives:

- 90% said they were taking more than one prescription medication a day and 32% said they need someone else to help them take their medicines or remind them to take them.
- A large proportion (69%) of patients reported that liver disease sometimes affects their ability to think clearly.
- Over half of survey respondents (51%) have been told they may require a liver transplant in the future.
- Half of respondents recorded having to take time off work for liver-related hospital appointments.

In addition, 40% of respondents noted they have to travel more than 25 miles to their liver centre/hospital for routine appointments. Having Fibroscan in primary care would therefore enable disease progression to be monitored locally with reduced hospital visits.

90% of all liver disease in the UK is attributable to alcohol, obesity and viral hepatitis and is therefore preventable.

Early detection is critical to enable intervention at a stage when remedial action/lifestyle changes can still have a chance of reversing damage and preventing disease progression.

Without early detection, patient outcomes are much bleaker: 75% of people with liver cirrhosis are diagnosed in a hospital or emergency setting when the disease has already progressed. By this time the options for treatment are limited.

2. How do symptoms and/or the condition or disease affect carers and family?

Liver disease can give rise to caring complications – with high care demands often arising in connection with advanced stages of the condition.

As highlighted in section 1, the prognosis for patients diagnosed late is particularly poor, and these patients are likely to need significant additional care as a result of their liver condition. The specifics will depend on the stage of disease but can include many tasks from driving patients to hospital appointments, managing medications to acting as a full-time carer.

For lifestyle-related liver disease, the mental and emotional pressure on carers is often exacerbated by the knowledge that the condition was preventable and there is added stress and anxiety due to stigmatisation.

Often, the primary care-giver will be an immediate family member, which can often give rise to financial pressures, especially if the patient can also no longer work.

Liver disease disproportionately affects the poorest and most vulnerable in society. Provision of care continues to be worse in the regions with the greatest socioeconomic deprivation and loss of life due to liver disease is also higher in areas of socioeconomic deprivation.

3. Are there groups of people that have particular issues in managing their condition?

Generally, the condition worsens as it progresses, but the lack of symptoms in early stages presents a barrier to early detection.

Early detection – and associated targeted intervention - can cause lasting behavioural change to reduce and remove risk of disease progression.

Once the condition is more advanced, then complications such as ascites, hepatic encephalopathy, portal hypertension and variceal bleeding present much more significant issues to manage.

Patients with advanced liver disease will face a requirement for more frequent hospital visits for treatment and may also find themselves unable to undertake normal day to day activities, not least the ability to work and drive.

Some liver disease patients may have addiction issues (either drug or alcohol).

Experiences with currently available technologies

4. How well do currently available technologies work?

Current practice sees a suite of procedures and tests used for detection, assessment and diagnosis of liver disease. Generally, these are initially liver blood tests, with ‘imaging’ technologies, including FibroScan being used at the next stage of the process.

Liver blood tests do not require the same level of trained resource to deliver, but not all liver blood tests provide accurate staging of disease progression. The merit of a technology such as FibroScan being included in the diagnostic package is that it provides insight into the current state of disease progression.

This knowledge enables healthcare professionals in primary care to manage the patient with much greater accuracy.

Patients with minimal/no liver damage can be given appropriate interventions and access to support services such as alcohol and weight management, leaving secondary care referrals solely for those with more advanced disease progression.

Fibroscan is one piece of the jigsaw and needs to be considered alongside other tests.

5. Are there groups of people that have particular issues using the currently available technologies?

Liver disease can be connected with chaotic lifestyles including, for example, alcohol dependency and IV drug use. These cohorts can be difficult to engage and often miss appointments, regardless of the technology involved.

For FibroScan to be used effectively across the population, the XL probe is required. Otherwise, people with higher BMI will be excluded from the pool of those who can be scanned. Even with an XL probe, there will be individuals, particularly those who are severely obese, from whom the FibroScan cannot obtain a valid reading.

About the medical technology being assessed

6. For those <u>with</u> experience of this technology, what difference did it make to their lives?

Fibroscan is one element of the 'diagnostic suite' but is a really important diagnostic marker that is a key tool in monitoring disease progression. If people can be diagnosed earlier and provided with appropriate lifestyle advice in primary care, liver disease progression can be halted or even reversed.

FibroScan has a number of features which make it beneficial to patients, namely:

- The exam process is simple and swift, requiring minimal preparation in advance and the exam itself taking up little (this reduces the likelihood of patients finding it difficult to attend)
- The process is non-invasive and painless, reducing stress and risk for the patient
- Results from the scan are available to the clinician with immediate effect – the test does not involve any lab analysis and associated delays this process may involve, meaning the patient is able to receive the results quickly (often at the time of the scan)
- The combination of ease/speed of exam and the ability to access results immediately can be motivational to patients – quick results enable immediate direct feedback from clinician to patient and the ability to use relevant interventions to drive behaviour and/or lifestyle change, including referral to support services including alcohol and weight management services

7. For those <u>without</u> experience of the technology being assessed, what are the expectations of using it?

We can comment on this from the perspective of attendees to our 'Love Your Liver' roadshows. Members of the public who attend these events usually have no significant prior knowledge of liver health risks, and therefore their understanding and experience of testing processes and technology is generally low.

After explanation of the purpose and process of the FibroScan test, roadshow attendees are almost unanimously reassured by the simplicity of the process, the fact that it is non-invasive, and the fact that results are immediate.

This latter point is of particular significance, as the ability to receive an instant result and associated advice and information is highly motivating.

8. Which groups of people might benefit most from this technology?

The cohort to benefit most is a significant one – those at-risk of liver disease but who have not been assessed / may not be aware of their at-risk status. This group would include:

- People drinking at potentially harmful levels (e.g. men who regularly drink over 50 units of alcohol per week and women who regularly drink over 35 units per week)
- People who may have put themselves at risk of contracting Hepatitis C
- People at risk of developing NAFLD (e.g. people with metabolic syndrome or those with type 2 diabetes)

All of these risk factor groups would see major benefit from the opportunity for early detection, as it would mean that:

- Any liver damage was identified earlier in the process as a result of the opportunity for a check being available within primary care
- This early detection would increase the likelihood of lifestyle changes being possible whilst the disease was at an early stage
- More serious cases would be identified earlier and fast-tracked to secondary care, with the associated improvement in patient outcomes compared to late detection in a hospital/emergency setting
- Fibroscan results are relatively easy for patients to understand and they report the results as being motivational in addressing lifestyle (losing weight, stopping drinking alcohol)

Additional information

9. Please include any additional information you believe would be helpful in assessing the value of the medical technology (for example ethical or social issues, and/or socio-economic considerations)

Key messages

10. In up to five statements, please list the most important points of your submission.

1. The use of FibroScan in primary care settings has the potential to deliver a much earlier detection point for people in at-risk sections of the population for liver disease. It also enables disease progression to be monitored without the need for extensive travel. The simplicity of FibroScan and its ease of accessibility, coupled with immediate delivery of results are all attractive features for patients.

2. Quick and immediate disease staging in a primary care setting enables swift delivery of accurate interventions and the chance to access relevant support services, particularly in the fields of alcohol and weight management.

3. The combination of points 1&2 is highly likely to lead to efficiency improvements by reducing unnecessary referrals to secondary care. More accurate detection and staging of liver disease at primary care level ensures that secondary care referrals are limited to those patients who require that level of specialist treatment and care.

4. The British Liver Trust is wholly supportive of increased early detection within primary care settings. GPs and other healthcare professionals in primary care are doing a fantastic job under a lot of pressure, but in many areas, they are working within a system that doesn't allow them to detect and treat liver disease effectively. This means that in many cases, people with liver disease are diagnosed far too late when treatment options are limited. 90% of liver disease is preventable and, in many cases, it's reversible if caught in time. That's why early detection and prevention are key.

5. The British Liver Trust believes every primary care provider should have direct access to a best practice fibrosis assessment, therefore improving the accuracy of disease assessment. The increased use of FibroScan as part of a suite of detection tools would represent a major step forward in this process, resulting in the opportunity for people at-risk of developing liver disease to have the best possible chance of having any liver health issues detected early, whilst opportunities for intervention and treatment are at their most effective and wide-ranging.

Thank you for your time. Please return your completed submission to diagnostics@nice.org.uk

External Assessment Centre correspondence log

GID-MT562 FibroScan

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who/ Purpose	Question/request	Response received
1.	22/09/2021	Collated EAQs received from NICE		Appendix 1
2.	22/09/2021	Company were contacted to confirm if Fibroscan can be used in children.	Hi [redacted] Please can you confirm if Fibroscan is licensed for use in children and if there is any age restriction when it is used in children? Kind regards, Tosin Oladapo	Dear Tosin Fibro Scan can be used to screen children, the probe selection will vary depending on the age and or the child's thoracic perimeter. Generally speaking, children under the age of 5 will likely need the "S" Probe in S1 mode, Children under the age of 10 "S" Probe in S2 mode. But the thoracic perimeter must be measured. In some cases children may need the M probe.

				I have attached our probe recommendation [Appendix 2] which covers this. Let me know if you have any further requests. Br [redacted]
3.	23/09/2021	Company were asked to provide information missing from the submission	Dear [redacted] I am contacting you from Newcastle External Assessment Centre (EAC) based at the Freeman Hospital in Newcastle. Our EAC has been commissioned by NICE to carry out the FibroScan assessment. NICE have forwarded your clinical submission, and we have a couple of queries we are hoping you can help with: • The submission included declarations of conformity for the 4 devices included in the assessment, but no CE certification – are you able to supply this as well? • The submission included instructions for use for 3 of the devices, but not for the 230 Go version – please can you supply this as well? Many thanks for your help Best wishes Emma	Dear Emma, Kim and Rachel, The company have provided the following additional documents as requested, please find a list below: • Probe recommendation document • CE mark document • User guide for the FibroScan go I've added the documents to the same NICE Docs link as the rest of the company submission here https://appraisals.nice.org.uk/request/146893 I think this is everything we've asked for to date, but please let me know if there is anything outstanding. Kind regards,
4.	24/09/2021	Additional information requested from Company	Dear [redacted] Please find attached some very basic initial questions [Appendix 3] from Newcastle EAC to support our assessment report. We would very much appreciate your responses. Just to confirm the process (I appreciate NICE have already communicated this to you), responses should be sent by email please. All correspondence that informs the assessment will be published in the correspondence log on NICE's website as supporting information when the final guidance is published. So please can you ensure that you highlight for redaction any information that is commercially sensitive ([redacted]) or academic in confidence ([redacted]). Many thanks for your assistance Best wishes	Responses not provided in advance of the Company call.

			Emma	
5.	05/10/2021	Company call	Initial questions (Appendix 3) and additional questions discussed with the Company during the company call.	Notes from call including written response from Company received 08/10/2021 (updated version received 13/10/2021 see below). Updated Clinical Evaluation Report (Mar 2021) supplied with written responses - Company have been asked to summarise, see below.
6.	12/10/2021	Additional information requested from Company	Dear [redacted] Thank you for the updated Clinical Evaluation Report (March 2021) which demonstrates equivalence of FibroScan 230 with FibroScan 630/530/430/502. The previous version of the Clinical Evaluation Report (Feb 2020) demonstrates equivalence between FibroScan 502 Touch/630/530/430 with D02, however can you confirm which versions were included in D02? We are lacking evidence to demonstrate equivalence to FibroScan 502 and FibroScan 402. The committee will require evidence that the devices in scope are equivalent to the devices used in clinical studies. The committee cannot be expected to read 2 lengthy CERs and, to help them, the EAC report will contain a succinct summary. We would like you to prepare a brief synopsis, ideally as a figure or table, which demonstrates this equivalence (between FibroScan 402 and 502, to FibroScan 630/530/430/230/503 Touch), which cites the CERs as required. We will review your table/figure and include it in our report (you will have an opportunity to review this during fact check). Ideally, the equivalence synopsis should be unredacted (the citations can be redacted if necessary). As the number of models (past and present) involved in this assessment is large compared with other technology assessments, we wish to avoid the committee identifying an uncertainty in equivalence, if none actually exists. Additionally thank you for your written responses to the EAC questions, however we note that a number remain unanswered (highlighted in pink	Updated responses received 13/10/2021, Appendix 4. Comparison table of devices received 12/10/2021 - Appendix 5 (part AiC) - full size Excel version available on request from NICE.

			in the attached). To avoid further delay, please can you submit written responses by COP today please? Many thanks for your help Best wishes Emma	
7.	13/10/2021	Expert Engagement Meeting		Notes from EEM - Appendix 6 Additional information received from expert (NG): In terms of the action point attributed to me. We have published the DNA rate for a “direct [redacted]
8.	29/10/2021	Additional questions to Experts		Questions to Experts with Collated responses - Appendix 7
9.	29/10/2021	Notes from Company Engagement Meeting (27/10/2021) with additional information from Company (provided 29/10/2021)		Appendix 8
10	01/11/2021	Additional query to the Company	Good morning, Thank you for providing the additional documentation, and apologies for coming back to you however the distinction between SmartDepth and SmartExam is still unclear. Can you please confirm if the below information is correct please? *A controlled attenuation parameter (CAP) is an optional measure of the attenuation of the ultrasonic signals (measured in dB/m) in tissue at a*	Hello Kim, Thank you for your email. The information below is correct, in red you will find the additional information based on Echosens product management team. I hope this will be helpful.

			frequency of 3.5 MHz (regardless of the probe used). The company launched SmartExam in 2021, which uses a new computation method of continuous CAP measurement (CAPc; also described in supporting documentation provided by the company as second generation CAP) throughout the vibration-controlled transient elastography examination, and SmartDepth which enables automatic depth selection based on the patient's morphology. The company claims that SmartExam permits deeper assessment of liver fibrosis and steatosis, extending probe to capsula distance from 35-75mm to 45-85mm when using the XL+ probe. SmartExam also automatically rejects measurements which do not meet validity criteria. The company has confirmed the first generation CAP measurement is available on FibroScan 502, FibroScan 502 Touch, FibroScan 530 Compact, FibroScan 430 Mini/Mini+, FibroScan 630 Expert and FibroScan 230 Go, and that second generation CAPc measurement is available on FibroScan 502 Touch, FibroScan 530 Compact, FibroScan 430 Mini+, FibroScan 630 Expert and FibroScan 230 Go. However, CAP and CAPc can only be measured with the M+ and XL+ probes. Also can you please confirm when the following models were stopped production or sale please? And can you confirm the replacement versions are correctly described in the below also: - FibroScan 402 stopped on **dd/mm/yyyy** (replaced by FibroScan 430) - FibroScan 502 stopped on **dd/mm/yyyy** (replaced by FibroScan 530) - FibroScan 430 Mini stopped on **dd/mm/yyyy** (replaced by FibroScan 430 Mini+) Many thanks Kim	Do not hesitate if you need any additional information Best regards Quentin A controlled attenuation parameter (CAP) is an optional measure of the attenuation of the ultrasonic signals (measured in dB/m) in tissue at a frequency of 3.5 MHz (regardless of the probe used). The company launched SmartExam in 2021, which uses a new computation method of continuous CAP measurement (CAPc; also described in supporting documentation provided by the company as second generation CAP) throughout the vibration-controlled transient elastography examination, and SmartDepth which enables automatic depth selection based on the patient's morphology. The company claims that SmartExam permits deeper assessment of liver fibrosis and steatosis, extending probe to capsula distance from 35-75mm to 45-85mm when using the XL+ probe. SmartExam also automatically rejects measurements which do not meet validity criteria. The company has confirmed the first generation CAP measurement is available on FibroScan 502, FibroScan 502 Touch, FibroScan 530 Compact, FibroScan 430 Mini/Mini+, FibroScan 630 Expert and FibroScan 230 Go, and that second generation CAPc measurement is available on FibroScan 502 Touch, FibroScan 530 Compact, FibroScan 430 Mini/Mini+, FibroScan 630 Expert and FibroScan 230

				Go. However, CAP and CAPc can only be measured with the S+, M+ and XL+ probes. Also can you please confirm when the following models were stopped production or sale please? And can you confirm the replacement versions are correctly described in the below also: - FibroScan 402 sales stopped on February 2017 at global level (replaced by FibroScan 430) - FibroScan 502 sales stopped on June 2015 at global level (replaced by FibroScan 530) - FibroScan 430 Mini sales stopped by end of 2021 in the UK (replaced by FibroScan 430 Mini+)
11	02/11/2021	Question to expert re ongoing studies	Good morning [redacted] Thank you for submitting your completed questionnaire to NICE. Within your responses you refer to the ongoing KLIFAD study. The EAC has been able to identify some information regarding the KLIFAD study (see Table below). However was unsure if KLIFAD was a subset of the ISRCTN16922410 (which states different recruitment targets etc).	Thanks. You have the right study The numbers I gave in my e mail were “ball park” we are on target to hit the 120 specified so feel free to change this figure. The primary and secondary outcomes are there (you have to go rather a long way down the document!), copied in below. I have added numbers and sites etc below Regards Steve

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
Does knowledge of liver fibrosis affect high-risk drinking behaviour (KLIFAD)? A feasibility randomised controlled trial - *identified by experts* UK (funded by NIHR RfPB) **Number of centres unknown** **No trial registration identified**	Ongoing Estimated completion date: end 2021	Target enrolment: 100 This study aims to determine the feasibility of adding FibroScan results to the advice given to people who drink high levels of alcohol, followed by watching an alcohol recovery video story.	**Not fully known** (includes drinking habits)	**Not reported**

For the KLAFID study are you able to provide a link to the trial registration (if available) or alternatively provide the information missing in the table please? Apologies for this additional request, but information on ongoing studies that may address current gaps in the evidence is always of interest to the Committee.

Many thanks
Kim

12	02/11/2021	Question to expert re ongoing studies	Good morning [redacted] Thank you for submitting your completed questionnaire to NICE. Within your responses you refer to two ongoing studies: 1) the scarred liver project and 2) the ID-Liver study. The EAC has been able to identify a number of outcome reports related to the Scarred Liver Project, but was unable to identify any prospective trial registration (including NCT or ISRCTN number) which documents the estimated completion date, target recruitment, primary and secondary outcome measures – see Table below.	Hi, The Scarred liver project is a programme of work that involves broad aspects of diagnostics, implementation and evaluation. As such it is not covered by one study registration. Here is the website – which give you a better idea. I do have a prospective cohort study which uses a broad range of liver diagnostic tests – also included. https://www.scarredliverproject.org.uk/ https://clinicaltrials.gov/ct2/show/NCT02037867 The ID liver project is a UKRI funded study , Clinical study details below – but again broader than a simple clinical trial https://clinicaltrials.gov/ct2/show/NCT04666402 The bottom line is that I have expertise and interest in broad diagnostic tests for chronic liver disease – FibroScan is one of those technologies. I have never received any funding for research from the company and I have not undertaken any consultancy for them Hope this helps [redacted]

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
The Scarred Liver Project – *identified by experts* **No trial registration identified**.	Ongoing Estimated completion date: **unknown**	Target enrolment: **unknown** New pathway combines non-invasive diagnostic tests (such as FibroScan) with actively seeking out patients at risk of chronic liver disease. Pathway accessible to more than 100 GP practices in East Midlands	**Not fully reported** (includes liver disease, cirrhosis)	**Not fully reported** (includes economic modelling, qualitative outcomes)
ID-Liver study – *identified by experts* **No trial registration identified**	**Unknown**	Target enrolment: **unknown**	**Not reported**	**Not reported**

			Are you able to provide a link to the trial registration (if available) or alternatively provide the information missing in the table please? Apologies for this additional request, but information on ongoing studies that may address current gaps in the evidence is always of interest to the Committee. Many thanks Kim	

Appendix 1

Additional information from collated EAQs:

			Response
1	Please describe your level of experience with the procedure/technology, for example: - Are you familiar with the procedure/technology? - Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? – Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	Expert #1	We utilise the fibroscan test for routine screening of all patients presenting to our NAFLD clinic in the secondary care setting. We have trialled the usage of this in the community in three large GP practices in patients with diabetes. This facilityis not available to primary care on a routine basis. This facility is utilised by all medical specialties in the hospital including diabetes, haematology, rheumatology and dermatology mainly.
		Expert #2	I am familiar with the technology and use it in my everyday practise. It is widely used in the NHS, I am not aware of any trust that does not use this technology. This technology is used in specialties such as general practice and hepatology (my own specialty)
		Expert #3	- Trained in Fibroscanning since 2009. - Using fibroscans in patients pre and post liver transplantation - It is usually used by gastroenterologists and hepatalogists - It is used regularly in secondary care and by some GPs with appropriate support and training.
		Expert #4	In my clinical practice as a GP I am involved in patient selection for Fibroscan with direct access to requesting the procedure based on triage in primary care. Using blood based scoring systems in those at risk of liver disease (usually for NAFLD or ARLD) fibroscans are requested and the results sent to us. The fibroscans are carried out in the hospital setting.Based on the results of the fibroscan the patient is either managed in primary care addressing risk factors by encouraging lifestyle modification or referred into hepatology for further assessment. I do not carry out fibroscans myself/they are not carried out in my GP practice but I am used to seeing and interpreting the results and acting accordingly. In previous clinical positions as a GP/trainee Fibroscan has not been available to request directly from primary care and ithas required a referral into gastroenterology or hepatology for them to consider carrying out a fibroscan. I have held clinical lead positions within the RCGP, currently as a clinical advisor and previously as the clinical champion for liver disease. Within this role we reviewed the evidence and published RCGP approved guidelines on the commissioning of services for people at risk of and living with liver disease. The use of Fibroscan within these recommendations is in line with NICE guidelines and can be found at: https://www.rcgp.org.uk/clinical-and-research/resources/a-to-z-clinical-resources/recommendations-for-commissioning-bodies-to-improve-the-early-detection-of-chronic-liver-disease.aspx See below research experience for knowledge around how widely Fibroscan is used in the NHS in the primary/community setting.
		Expert #5	- Are you familiar with the procedure/technology? YES - Have you used it or are you currently using it? YES – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? MOST HOSPITAL HAVE A FIBROSCAN – THESE WERE BOUGHT WHEN HCV TREATMENT TRAILS WERE BEING CONDUCTED. ALL OPERATIONAL DELIVERY NETWORKS WILL HAVE ONE OR TWO FIBROSCANS.I AM NOT AWARE MANY GPs/CCGs HAVING ONE. SOUTHAMTON AND EAST HAMPSHIRE HAVE ACCESS TO ONE I KNOW

			– Is this procedure/technology performed/used by clinicians in specialities other than your own? ONLY USED FOR PATIENT WHERE LIVER DISESE IS SUSPECTED – BUT RHEUMTOLOGY, DERMATOLOGY AND CYSTIC FIBROSIS TEAM USE OUR MECHINE If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it. I AM A HEPATOLOGIST AND WE HAVE OUR OWN
		Expert #6	• I am highly familiar with this procedure / technology having been integral to establishing over 12 years 2007-2019 the largest Fibroscan service within the NHS • I have use and performed Fibroscan since 2007 and currently use the latest fibroscan equipment with SmartExam with continuous CAP technology. • Fibroscan is used as a standard of care in only those areas with access to it. This is primarily only specialised Hepatology areas, some gastroenterology, Drug and alcohol. • Access to Fibroscan can be driven by full-service development with all areas where liver health is an issue – Endocrinology, cardiology, obesity care - to achieve this the challenge is the training, staff resources and equipment needs • This procedure is primarily delivered through nurses and technicians. It can be performed by clinicians spending additional 10-20 minutes per consultation. The current guidelines (EALS 2021) recommend a minimum of 100 scans to be proficient. Regular scanning is also recommended by Echosens the manufacturer of the technology. • We accept self-referrals from members of the public as part of lifestyle and wellbeing assessments. • We also receive and accept referrals from all health and lifestyle specialities and practitioners • I am a provider and developer of fibroscan delivery services which includes the whole service – equipment, trained scan staff and reports to the referrer with the addition of being fully CQC regulated for this technology and service
		Expert #7	I have a research interest in chronic liver disease and early detection in the community I have conducted research in community settings utilising the fibroscan as part of liver health assessment
		Expert #8	- Are you familiar with the procedure/technology? **Yes** - Have you used it or are you currently using it? **Yes** – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? **Widely used in secondary care but not primary care** – Is this procedure/technology performed/used by clinicians in specialities other than your own? **Very rarely** – If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it. **No**
		Expert #9	I am familiar with the technology and it is in use routinely in my practice. Uptake is patchy across the UK, there is evidenceto support this with many ICS/CCG areas not having liver pathways with fibrosis assessment in them. It is not performed routinely by specialty groups outside hepatology I am not involved in referral on, fibroscan is used to assess referrals into the hepatology service

2	Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1	I have done clinical research on this procedure involving patients or healthy volunteers.
		Expert #2	I have had no involvement in research on this procedure.
		Expert #3	I have done bibliographic research on this procedure.

	• I have done bibliographic research on this procedure. • I have done research on this procedure in laboratory settings (e.g. device-related research). • I have done clinical research on this procedure involving patients or healthy volunteers. • I have published this research. • I have had no involvement in research on this procedure. • Other (please comment)	Expert #4	I have done bibliographic research on community liver disease pathways in the UK. I have brought together evidence onthe clinical and cost effectiveness of various community detection pathways some of which have involved the use of Fibroscan as part of a community pathway. I have published this research at : https://doi.org/10.3399/bjgp21X715553 I have also argued in peer reviewed GP readership editorials for more comprehensive management of liver disease in primary care and the role that Fibroscan may play in this and the costs involved according to NICE recommendations on NAFLD: https://doi.org/10.3399/bjgp17X690557 I have done health services research on how widespread the use of Fibroscan is within CCGs/Health Boards within the UK as part of liver disease management in primary care. This national survey (in collaboration with the British Liver Trust) indicated that nationally 25% of CCGs/Health Boards were using Fibroscan as part of their endorsed primary care detection pathways. The findings of this survey are available at: https://doi.org/10.3399/BJGPO.2021.0085
		Expert #5	I have published this research.
		Expert #6	In a previous role I have devolved and delivered research scan processes and procedures Audited fibroscan services and assisted in the evidence base for inter and intra operator variability
		Expert #7	I have done clinical research on this procedure involving patients or healthy volunteers. **Yes** I have published this research. **Yes.**
		Expert #8	I have done bibliographic research on this procedure. **Yes** I have done research on this procedure in laboratory settings (e.g. device-related research). **No** I have done clinical research on this procedure involving patients or healthy volunteers. **Yes** I have published this research. **Yes** I have had no involvement in research on this procedure. **No**
		Expert #9	I have done bibliographic research on this procedure. **Yes** I have done research on this procedure in laboratory settings (e.g. device-related research). **Not in development of the device but in validation of it in clinical populations** I have done clinical research on this procedure involving patients or healthy volunteers. **Yes** I have published this research. **Yes** I have had no involvement in research on this procedure.Other (please comment)

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design?	Expert #1	Established practice in secondary care and no longer new as a technology but limited use in primary care.
		Expert #2	This procedure is current standard of care, this saves biopsying patients to gain a reading of cirrhosis. Established practice and no longer new.

		Expert #3	The technology is simple and easy to apply. The results are also easy to apply to patients. Established practice and no longer new.
	Which of the following best describes the procedure (please choose one): • Established practice and no longer new. • A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. • Definitely novel and of uncertain safety and efficacy. • The first in a new class of procedure.	Expert #4	The use of Fibroscan is established practice in the hepatology setting and it is becoming more normalised to be able to request Fibroscan directly from the primary care setting although this is still not available across the whole of the UK. There are several areas where Fibroscans are now being carried out and interpreted within the community setting, with referrals to secondary care being based on the result of the Fibroscan. As such it is already an established procedure withavailability limiting wider role out rather than the novel nature of the procedure.
		Expert #5	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? STANDARD CARE IS LIVER PATIENTS WILL HAVE LIVER FIBROSIS ASSESSED IN THE HOSPITAL WITH INCREASED COSTS. THIS TOOL BEING AVAILABLE TO PRIMARY CARE WILL REDUCE THE BURDEN ON HOSITAL OUTPATIENT CLINICS BUT ALSO PICK UP LIVER DISEASE EARLIER. Established practice and no longer new. IT IS ESTABLISED PRACTICE FOR USE IN SECONDARY CARE A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. I AGREE
		Expert #6	The technology is currently the only point of care non-invasive technology which is not blood based. It has high patient engagement unlike biomarkers and does not rely on the liver having to have an abnormal enzyme which is often uncommonin liver related issues resulting in late presentation and diagnosis It is not only in >2500 peer reviewed publications but also now in >70 international guidelines. EASL recent non-invasive guidelines recommend access at primary care level as Fibroscan can be delivered in most settings. It has a high negative predictor for advanced fibrosis which is the most significant indicator of prognosis and outcome. **Established practice and no longer new.** **Of note it is only standard and established practice in secondary care specialist Gastro / Hepatologysettings** **It is not standard or established practice in any other area or areas with high liver related comorbidconditions – Endocrinology, Cardiology, obesity medicine and Rheumatology**
		Expert #7	Fibroscan has provided an alternative approach to diagnosis of liver fibrosis which avoids a potentially risky liver biopsyand hence has gradually become incorporated into usual care.

			Established practice and no longer new.
		Expert #8	Compared to liver biopsy this technology is innovative and novel Which of the following best describes the procedure? **The first in a new class of procedure. (In comparison to liver biopsy)**
		Expert #9	Established practice and no longer new. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. Safety and effectiveness is established-it is however poorly taken up Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.

4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1	It will cut down referrals to secondary care
		Expert #2	As the process evolves so more disease activity will be monitored by this innovation
		Expert #3	Addition to SOC
		Expert #4	Fibroscan would be used as a addition to current standard of care in the primary care setting and act to shift and potentially reduce the need for referral to more specialist services. Rather than referrals being made on the basis of blood markers (which have a very good negative predictive value for ruling out liver disease but a poorer positive predictive value for ruling in significant disease), those with high risk blood markers would have a Fibroscan in the primary care setting and referrals would be made based on a high chance of advanced fibrosis/cirrhosis as detected by the Fibroscan. Fibroscan could be used to replace current standard care - i.e. all those with liver disease risk factors for NAFLD or ARLD could do straight to Fibroscan. This does not seem to make sense due to the low cost and high negative predictive value of the blood based fibrosis markers it would make sense for Fibroscan to sit after these tests in a 2 stage process.
		Expert #5	STANDARD CARE IS LIVER PATIENTS WILL HAVE LIVER FIBROSIS ASSESSED IN THE HOSPITAL WITH INCREASED COSTS. HOWEVER, THIS WOULD STILL BE AVAILABLE THIS TOOL BEING AVAILABLE TO PRIMARY CARE WILL REDUCE THE BURDEN ON HOSITAL OUTPATIENTCLINICS BUT ALSO PICK UP LIVER DISEASE EARLIER.
		Expert #6	Fibroscan has the potential to augment and improve the detection of liver disease and those at high risk of early mortality and expensive treatments in the near future. If access is encouraged and facilitated to high-risk disease areas – Type 2 diabetes, dyslipidaemia hypertension, obesity care. Fatty liver disease alone is estimated to account for 1:4 of thepopulation and rising with adolescents and young adults at growing risk.
			Early detection enables risk stratification and improves early management options in which are not currently available despite growing evidence

		Expert #7	See above
		Expert #8	Yes
		Expert #9	Yes, would able stratification of risk and change standard care very significantly

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1	Graded assessment using blood tests and scoring systems and dependency on secondary care for risk stratification of patients
		Expert #2	It has replaced many indications for biopsy such as in the treatments of hepatitis C and B and is now standard of care for these diseases
		Expert #3	Liver biopsy is something that is defined as the 'Gold standard' but this is not applicable to Primary care. At present primary carehave to refer to secondary care for a fibroscan.
		Expert #4	In the primary care setting those with abnormal liver function tests or fat on a liver ultrasound are investigated for causes of liverdisease using regional or nationally agreed guidelines for the interpretation of liver blood tests. Once rarer causes of liver disaese have been ruled out this would usually involve some assessment of stage of liver damage using a test to look for advanced fibrosis/cirrhosis. This would usually be a blood based algorithm test such as the Fib4 or NAFLD fibrosis score test. If the results of these tests show a high risk then the patient is referred onto a specialist unless there is availability of Fibroscan (orother transient elastography technology) available in the community. If any other cause of liver disease other than NAFLD or ARLD is suspected (e.g. viral or autoimmune causes) then the patient is referred directly to secondary care without further fibrosis assessment. In some areas people at high risk of ARLD or NAFLD are being investigated with serum fibrosis markers regardless of their initialliver blood tetsts, just based on thier risk factors for liver disease. This is not yet current standard of care in the NHS but is becoming increasingly common. This case finding in high risk individuals is felt to be necessary by some due to the fact that many people with advanced liver disease may have normal routine liver blood tests but still score highly on the serum fibrosis testing/have abnormal Fibroscan results - i.e. significant liver disease can be missed by relying on LFTs alone.
		Expert #5	STANDARD CARE IS LIVER PATIENTS WILL HAVE LIVER FIBROSIS ASSESSED IN THE HOSPITAL WITH INCREASEDCOSTS. THIS TOOL BEING AVAILABLE TO PRIMARY CARE WILL REDUCE THE BURDEN ON HOSITAL OUTPATIENT CLINICSBUT ALSO PICK UP LIVER DISEASE EARLIER.
		Expert #6	The primary SOC remains the detection of an abnormal liver enzyme, and the use where they are done of current guidelines (NICE or local) If this is followed a specialist referral is made and where a centre has access to Fibroscan this may be performedat or after the appointment.

		Expert #7	(Not answered)
		Expert #8	Very heterogenous pathways of care in primary care – very confusing landscape
		Expert #9	Blood tests which do not give detailed information of liver fibrosis resulting in referral into secondary care for many people without evidence of significant liver fibrosis. The opposite is also true that this reliance of liver enzyme levels leads to many people with cirrhosis failing to be identified with an acute presentation of decompensated disease being the result-currently 50%in UK practice. This deprives patient of early diagnosis and the potential for lifestyle interventions to avoid that risk.

6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1	Acoustic Radiation Force Impulse US Imaging (ARFI) which can be factored in during routine ultrasound assessment.
		Expert #2	I am not aware of anything similar
		Expert #3	ARFI but this is usually performed by a radiologist.
		Expert #4	No
		Expert #5	ULTRASOUND BASED SHEARWAVE – ONLY AVAILABLE IN SECONDARY CARE WHERE THE RADIOLOGY DEPARTMENT IS BASED – PATIENTS WOULD HAVE TO COME TO HOSPITAL THIS TECHNOLOGY IS NOT GOING TO BE PRACTICAL TO USE IN PRIMARY CARE
		Expert #6	All other modalities are not point of care MRI, CT, MRE, MRI-PDFF Biomarkers for liver disease often require an abnormality in an enzyme - where this is the situation and the correct enzymesare requested – there is currently NO standardised liver blood profiles used in primary care AST or ALST are not standard requests - Fib-4 is the first line, NAFLD fibrosis score, ELF can also be used with recommendation with cut off values. Fibroscan is then a recommended 2nd / 3rd line assessment where it is available. Sequential liver assessment is advocated to reduce the indeterminate zone, this remains however in the minority of those with liver disease and poor liver health given the current low level of identification with biomarkers.
		Expert #7	Liver fibrosis blood markers Ultrasound CT MRI scan Liver biopsy
		Expert #8	Multiple technologies including serum markers of fibrosis (ELF) and MRI. The latter is not currently ready for diffusion into primary care.
		Expert #9	ELF test. Blood test but performs similarly in fibrosis detection. Some pathways use this rather than fibroscan with some advantages and drawbacks to both.
7	What do you consider to be the	Expert #1	Less visit to secondary care and diagnosis closer to home

	potential benefits to patients from using this procedure/technology?	Expert #2	Cheaper to use, safer for the patient than a biopsy, non-specialist to use (health care assistants can operate thistechnology) Accessible to all, no limitations on use
		Expert #3	Identification of patients with moderate fibrosis and likewise excluding those with minimal fibrosis.
		Expert #4	Allow patients to have a more definitive test for liver fibrosis/cirrhosis in the community avoiding the need for a wait for a secondary care appointment that may not be needed. Diagnose their significant liver disease earlier allowing them the chance to make appropriate lifestyle changes to prevent progression Diagnose cirrhosis earlier allowing patients to be regularly screened for HCC and screened for varices. Diagnose significant liver disease earlier allowing patients to participate in clinical trials of new treatments that may prevent fibrosis progression.
		Expert #5	ACCESSABLE LOCALLY TO THE PATIENT WITHOUT HAVING TO TRAVEL TO HOSPITALEARLY DETECTION OF LIVER FIBROSIS INTERVAL MONITORING FOR PROGRESSION OF LIVER DISEASE AND OPPORTUNITIES TO PROVIDE BRIEF INTERVENTIONS
		Expert #6	There is growing evidence to support the following: Early detection of a liver and individual at risk for review and management planning,Ability to add to common biomarkers Fibroscan & AST = FAST Complex comorbidity management in primary care for patients with pre-diabetes, type 2 diabetes, obesity, CVD or on medications that are hepatotoxic or promote fatty liver disease – i.e. – Tamoxifen or methotrexate. Cost effective management and care in those >40 with Type 2 diabetes (T2DM) Increased awareness of liver health and its relationship to high-risk non-communicable diseases High patient engagement in their own health management and lifestyle alterations – alcohol reduction Continued weight loss maintenance, monitoring of improving or deteriorating liver health There is strong evidence in a few primary care locations where direct GP access to fibroscan improves the pathway, reduces referrals, reduces cost per patient by approximately £550, removes >90% from the referral pathway enabling the most appropriate patient to access specialist care – Nottingham, Solent Health, Southampton, Oxford, Newcastle and Birmingham. These areas have developed from a hepatology base with the strength in the disease. This is not currently available in primary care Not all of these provide Fibroscan in primary care and patients travel to the secondary care location
		Expert #7	Avoidance of potentially risky biopsy Repeat scans for monitoring purposes
		Expert #8	Improved access to diagnostics and specialists at a stage when liver disease is reversible,

		Expert #9	Early diagnosis in those at risk and stratification of risk.

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1	Patients who have to travel long distances
		Expert #2	Community patients. No need to come into hospital if they could access it in a diagnostic hub or GP practice. If themachine is portable this could be taken to the community/pharmacy/supermarket to capture more potential patients
		Expert #3	Diabetics. Patients with NAFLD
		Expert #4	All patients at risk of significant liver disease.
		Expert #5	IN PRIMARY CARE - PATIENTS WITH ALCOHOL USE DISORDER AND PATIENTS WITH FATTY LIVER DISEASE RELATED TO METABOLIC CONDITIONS
		Expert #6	As this is a quick and safe procedure all people could benefit with the establishment of fibrosis and liver fat assessment to rule in or out poor liver health as a risk. CVD is the highest cause of death in those with fatty liver which accounts for 1 in 4of the population with > 16million in the UK estimated to suffer from this. It is currently those with F3/F4 fibrosis at the highest risk of mortality and survival. Although new evidence suggest that even simple steatosis increases mortality and shortens life expectancy. It is the impact of fatty liver in the metabolic conditions and the bidirectional relationship with type 2 diabetes. Improved detection of liver fibrosis is required in 2021 Liver and pancreatic cancer have taken over from vascular disease as the biggest cause of excess death in those with diabetes – which Fibroscan can screen, and risk stratify in this population Other high-risk populations • NASH and NAFLD • Obesity in adults, in children and adolescents • Those with individual components or combined Dyslipidaemia, Hypertension and Type 2 diabetes • BMI > 23 in certain ethnic groups – Asian, South pacific islander, Hispanic • Viral hepatitis C, B • High alcohol consumption • Women's Health - Polycystic ovary disease, post-menopausal • Medications of concern – Tamoxifen, Methotrexate, corticosteroids • Past family history of liver cirrhosis
		Expert #7	(Not answered)
		Expert #8	Broad application to all chronic liver disease
		Expert #9	Heavy drinkers and those with metabolic syndrome.

9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1	Yes as highlighted above
		Expert #2	Alongside liver health pathways for the GP this technology could detect early liver disease to be targeted for treatments, preventing long term health problems and costs to the NHS It could rule out significant liver disease also so reducing down the referral rate to hospital care.With 1-stop clinic, we could diagnose, advise and discharge lifestyle management portals
		Expert #3	Yes. Adoption of this in primary care will help reduce referrals to secondary care.
		Expert #4	As above - if Fibroscan is carried out in the community before referral to secondary care it could reduce referrals by providing a better community test that can positively predict advanced fibrosis and cirrhosis and avoid the need for all those with abnormal blood markers to be referred. Potential for fewer hospital visits if carried out within the community.
		Expert #5	STANDARD CARE IS LIVER PATIENTS WILL HAVE LIVER FIBROSIS ASSESSED IN THE HOSPITAL WITH INCREASED COSTS. THIS TOOL BEING AVAILABLE TO PRIMARY CARE WILL REDUCE THE BURDEN ON HOSITAL OUTPATIENTCLINICS BUT ALSO PICK UP LIVER DISEASE EARLIER. ACCESSABLE LOCALLY TO THE PATIENT WITHOUT HAVING TO TRAVEL TO HOSPITAL EARLY DETECTION OF LIVER FIBROSIS INTERVAL MONITORING FOR PROGRESSION OF LIVER DISEASE AND OPPORTUNITIES TO PROVIDE BRIEF INTERVENTIONS
		Expert #6	Yes – Early detection and identification of those with poor liver health and fibrosis F3/F4 offer immediate potential to stabilise, improve and reversed disease thus affect mortality rates Placing skilled fibroscan staff in primary care will increase the knowledge base in an area where there is poor awareness of liver related conditions outside of alcohol or hepatitis which can often be stigmatised and profiled Early detection of poor liver health related to high fat / steatosis can assist in the implementation and support of lifestyle alterations and prevention improvement in high-cost associate diseases T2DM, CVD

			Liver health and disease location prevention and comorbid condition management offers significant potential to streamline and improve the care of the whole person not individual disease management with duplication and appointment processesin the wake of COVID-19, person centric models offer potential. In areas highlighted above UK evidence demonstrates the reduction in appointments in the specialist pathway, improved quality of referrals to the specialist areas, early location assists cancer monitoring, management and early detection which enables cheaper management options. There is strong evidence in a few primary care locations where direct GP access to fibroscan improves the pathway, reduces referrals, reduces cost per patient by approximately £550, removes >90% from the referral pathway enabling the most appropriate patient to access specialist care – Nottingham, Solent Health, Southampton, Oxford and Birmingham. These areas have developed from the hepatology base with the strength in the disease. This is not a situation which is currently available in primary care
		Expert #7	Yes it could be incorporated into a liver diagnosis pathway and enable community management of early liver disease with appropriate follow up
		Expert #8	Yes
		Expert #9	Yes-see above. It would reduce hospital clinic attendances for those with minimal or no liver disease and allow early identification of those at high risk.

10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1	Much less if societal costs are measured and will be less carbon footprint too.
		Expert #2	This technology would save money by reducing down the referrals to secondary care for investigation of abnormal liver blood tests. A cycle of fibroscanning could be used to monitor liver health rather than repeated visits to hospital clinics. Inthe long term, those diagnosed with liver disease would have early intervention to prevent long term co-morbdity. We already provide fibroscan clinics in hospital with a HCA, why not put this in the community reducing capacity in hospital, improving access to the technology and education to the public.
		Expert #3	Cost more initially
		Expert #4	If Fibroscan is available in the community and nothing else within the pathways of care changes then it is likely to cost less that current standards of care as the Fibroscan will prevent a significant number of secondary care referrals. This is assuming GPs/other primary care team members are aware of the availability of scans and the criteria for requesting. If the availability of Fibroscan in the community means more primary care teams are more proactive at finding their patientsat risk of liver disease beyond those with abnormal liver blood tests then more significant liver disease may be detected leading to short term increase in costs as scan demand is high and there are significant new numbers with advanced fibrosis and cirrhosis being referred onto secondary care. This should lead to long term savings in reducing emergency admissions with decompensated cirrhosis but I don't think the long term impact evidence is there.
		Expert #5	IN SOUTHAMPTON THE TECHNOLOGY IS HIRED AND NOT BOUGHT OUTRIGHT. THIS HAS BEEN FINANTIALLY BENEFITIAL AS IT HAS REDUCED THE NEED FOR HOSPITAL APPOINTMENTS

		Expert #6	SOC - Bio markers where there are abnormal enzymes offer low-cost assessment – there is no unification and standardisation of blood requests for liver disease. There are low detection rates for liver disease on current guidelines even where followed - liver enzyme tests cannot be used to rule in or rule out disease Capital investment in equipment can now de done with Echosens in cost per scan options or the full purchase of equipment. The additional costs of training, supervision of new staff or skilled operators need to be accounted for with associated on cost, location costs. These are currently under assessed and may be considerable with the implementation in primary careif all Cost per fibroscan through the tariff system can currently be >£700 with 90% referred to primary care for local management. This cost saving has been demonstrated by UK care models. Fibroscan is primarily delivered by nurse specialist although technicians can be used. Purchase of equipment offers benefits although there are other benefits available form pay per scan models which will be based on minimum scans per month. The volume of scans impacts the cost per scan and the comparative cost depending on the model of choice. Tenders from Independent providers / contractors can offer cost savings as they hold all capital costs including machines, probes and staff and can provide additional volume-based options.
		Expert #7	Less than current pathway involving liver biopsy
		Expert #8	Published evidence that this technology is cost effective when applied in primary care settings now exists
		Expert #9	Yes, there is a cost effectiveness analysis which confirms it is a highly cost effective intervention.

11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1	Cost of equipment and annual maintenance
		Expert #2	Community practise. This would be the cheaper than a GP consultation, staffed by a consultant nurse specialist in the community to scan the patient and give advise depending on the level of fibrosis seen. Most patients would have a brief intervention with lower fibrosis scores, but with the ability to refer to specialist clinics if needed Hospital 1 stop clinic. This would cost the same for an initial visit to a hospital consultant but with the benefit of having all the information in one go. It would be staffed by consultant nurse in liver, the fibroscan machine and a specialist dietician with the ability to refer to diabetic/lipid clinic

		Expert #3	Cost more
		Expert #4	As most areas do not have fibroscan within their community pathways at present there will be initial resource impact of buying the scanning equipment and training staff to use it. It will therefore cost more that standard care in the primary care setting.
		Expert #5	NURSES NEED TO BE TRAINED TO USE THE MECINE AND PROVIDE THE BRIEF INTERVENTION. THIS STILL COSTS LESS THEN ATTENDING HOSPITAL OUTPATIENT APPOINTMENT
		Expert #6	Fibroscan currently has limited availability through specialist areas so the possible initial impact to implement and staff new services and referral pathways could be lengthy and high. Once established ongoing costs can be managed and forecast. Introduction to primary care as a location will depend on the model to be implemented - impact reviews and assessments in relation to who will scan, level of training – EASL recommendations (2021) recommend a minimum of 100 scans to be proficient. Models based on outreach from secondary care deliver skilled operators and knowledge and are currently limited to those areas with specialist services and as such are costly on a per scan basis. Capital investment for staffing including administrative and training would need to be assessed and increase accordingly to provide increased services and these costs picked up from the providing trust. Referral pathways and location of services – in primary care practice locations, polyclinics, diagnostic hubs, through mobile scan clinic vans or in secondary care
		Expert #7	If adopted the technology could offer more widespread access to accurate liver diagnosis and appropriate management either through specialist services or primary care.
		Expert #8	Capital investment in primary care will offset costs in secondary care
		Expert #9	About the same, there is a cost for the machine and training plus servicing but this is likely offset by not seeing in secondary care a large number of people with mild disease

12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1	Needs to be housed in a clinic room and will need training
		Expert #2	None – all that is needed is a room and a couch
		Expert #3	Fibroscan machine, patient couch
		Expert #4	Training is the main change needed. Facilities are adequate if room availability there. Likely would sit better in a community diagnostic hub or group of practices setting rather than being cost effective to have a Fibroscan and trained operator in every GP practice as the numbers needing fibroscan unlikely to be sufficient to make this cost effective.

		Expert #5	A CLINIC ROOM AND BED
		Expert #6	Dependant on the model of delivery minimal if any changes would be required Fibroscan models 530 and 430 mini plusare highly mobile offering all locations form nursing homes, primary care rooms or even the patient's home. Infection control and PPE requirements can be accommodated.
		Expert #7	(Not answered)
		Expert #8	Very minimum
		Expert #9	Somewhere patient can lie flat with right chest wall exposed, takes around 10 minutes and has no clinical risks.

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1	Yes
		Expert #2	Training is needed to make the procedure efficient, there are no safety concerns. Training is certificated in order to insurethe equipment in case of damage.
		Expert #3	Yes. Training with Echosens (manufacturer)
		Expert #4	There is standard training available from Echosens for operators and also from others already experienced in using the technology. I am not an expert in this area and do not carry out Fibroscan.
		Expert #5	ONE DAY TRAINING IS NEEDED FOR THE PERSON PERFORMING THE FIBROSCAN
		Expert #6	Initial training is delivered only by Echosens, and certification provided for this. Staff who are not trained in accordancewith minimal device requirements may affect governance and accuracy of fibroscan. Fibroscan training can be delivered to non-healthcare staff however the requirements of the clinic where this model is used often requires a second appointment /consultation EASL have defined in the recent non-invasive guidelines (2021) a minimum of 100 scans to be proficient – this requires highly skilled staff to be able to monitor, supervise and educate staff on fibroscan techniques in a variety of challenging populations, children, adolescents and obese. The reading of the elastograms and the recognition of poor but technically valid scan is required to reduce errors andfalse negatives and positives.
		Expert #7	(Not answered)
		Expert #8	Some training required - standard SOPs exist
		Expert #9	Yes, there is an on line training package (2 hours) and 20 procedures required to achieve competence.

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1	Cannot be used in pregnancy (relative)
		Expert #2	An incorrect reading would give false reassurance or suggest significant damage causing emotional distress False low/high readings, or difficulty obtaining a reading. Occasionally needing a repeat of the procedure As far as I am aware there are no adverse events in the literature
		Expert #3	Not recommended in patients with a permanent pacemaker
		Expert #4	No direct harms - safe procedure. Not aware of adverse events in the literature. Failure rates are higher in the morbidly obese so potential harm from failed procedure and wasted appointment/stress this may cause patients while waiting for another test/procedure. Can be avoided by having clear guidelines on when/who to request Fibroscan on.
		Expert #5	What are the potential harms of the procedure/technology? NONE Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) NONE Anecdotal adverse events (known from experience) NONE Theoretical adverse events NONE
		Expert #6	There are no documented potential harms from Fibroscan The equipment is user friendly and cleanable with clinell wipes for infection control, it is a one-dimensional ultrasound device which requires CQC regulation Fibroscan is safe in pregnant women, children and those with implanted medical devices. Fibroscan is also suitable in all ethnic groups and in for those with disabilities. On occasion it may cause minimal bruising at the rib space used but this is infrequentThere are no lifetime accumulation affects related to fibroscan
		Expert #7	(Not answered)
		Expert #8	There are negligible harms and they do not have clinical significance
		Expert #9	The only harm could be in reducing motivation for lifestyle change in those with mild or no liver injury but this is a very low risk. There are really no serious risk or adverse events otherwise.

15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1	Easier pathway and reduced hospital referrals
		Expert #2	Monitoring the effects of lifestyle changes on fatty liver Monitoring efficacy of treatments for liver diseases such as hepatitis C Encouraging harmful drinkers to reduce by giving real time data
		Expert #3	Number of referrals to secondary care Identifcation of patients with advanced fibrosis that are asymptomatic/normal liver bloods
		Expert #4	measure of stiffness of the liver in KPa as an estimate of fibrosis/cirrhosis level in the liver
			fat content of the liver

		Expert #5	REDUCE SECONDARY OUTPATIENT APPOINTMENTS ACCESSABLE LOCALLY TO THE PATIENT WITHOUT HAVING TO TRAVEL TO HOSPITAL EARLY DETECTION OF LIVER FIBROSIS
		Expert #6	The following are possible Immediate results Early detection of possible advanced fibrosis for investigation The high negative predictive value for no significant fibrosis Identification of liver fat levels to assist in stratifying those at risk of T2DM, increased CVD risks, Liver risks Identification of those who lifestyle modification would be advised – ability to monitor and quantify weigh loss internally Motivational intervention opportunity – high level of patient engagement Risk assessment and monitoring opportunities Detection of those at highest risk of liver cancer for enhanced monitoring Improved treatment and management options Ability to add AST to fibroscan = FAST score in primary care to predict NASH and reduce liver biopsy requirements
		Expert #7	(Not answered)
		Expert #8	Diagnosis of cirrhosis Health economic Behaviour change (which my impact on other co-morbidity)
		Expert #9	Liver Fibrosis measurement

16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1	None
		Expert #2	Does telling harmful drinkers that they have minimal liver damage with this technology encourage them to carry on withtheir hazardous behaviour
		Expert #3	Nil
		Expert #4	none aware of other than it’s efficacy in those with very high BMI
		Expert #5	IN PATIENT WITH VERY HIGH BMI, THIS PROCEDURE IS HARDER TO PERFORM
		Expert #6	Positive and negative predictive values are considered acceptable increasing with various cut off values in diseasespecific areas
		Expert #7	The key issue is over accuracy of diagnosis and relationship to prognosis. The value of repeat scans, the appropriate frequency of repeat scans.
		Expert #8	Long term outcomes in primary care setting
			Serial measurement
		Expert #9	There is a learning curve. About 5-7% of patients, particularly those with truncal obesity, may not return a valid score

17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1	Difficult in patients with high BMI
		Expert #2	Does telling people they have significant liver disease cause them harm to their mental health when they were lookingfor reassurance in the community setting?
		Expert #3	No
		Expert #4	No
		Expert #5	I AM NOT AWARE OF ANY
		Expert #6	NO - Fibroscan is highly recommended and is increasingly guideline approved for increased access and use in primarycare EASL, APASL As screening and with additional investigations
		Expert #7	(Not answered)
		Expert #8	Not really
		Expert #9	No

18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one): • Most or all district general hospitals. • A minority of hospitals, but at least 10 in the UK. • Fewer than 10 specialist centres in the UK. • Cannot predict at present.	Expert #1	Most or all district general hospitals and large general practices.
		Expert #2	Most or all district general hospitals.
		Expert #3	Most or all district general hospitals. I don't think all GP surgeries will perform this but may have a referral surgery within their patch/area
		Expert #4	As this is about the use of Fibroscan in primary care the options given not really relevant. It is already being used in all tertiary liver centres, many DGH hospital settings and a few community settings. If being used as part of primary care pathways it would make sense for operator expertise, space availability and to ensure the scanner is well used for it to be able to be requested from every primary care premises but actually carried out in community diagnostic hubs or shared centres where many practices can refer . These may or may not be housedin hospital sites and could be spread more across regions if demand increases.
		Expert #5	Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. **YES** Fewer than 10 specialist centres in the UK.Cannot predict at present.
		Expert #6	**Most or all district general hospitals** **This is also suitable for all primary care locations, health settings, gyms, lifestyle medicine locations, screening locations**
		Expert #7	Most or all district general hospitals.

		Expert #8	**Most or all district general hospitals.** A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.
		Expert #9	Most or all district general hospitals. **Yes, indeed it is suitable for community use** A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #1	BMC Gastroenterology volume 19, Article number: 122 (2019) https://doi.org/10.1371/journal.pone.0251741
		Expert #2	A nurse-led Fibroscan outreach clinic encourages socially deprived heavy drinkers to engage with liver services.Matthews, MacGilchrist, et al Clinical journal of nursing 28 (3-4), 650-662, 2019
		Expert #3	(Not answered)
		Expert #4	(Not answered)
		Expert #5	(Not answered)
		Expert #6	1. Lazarus, J.V., et al., *Defining comprehensive models of care for NAFLD.* Nat Rev Gastroenterol Hepatol, 2021. 2. Alam, M.S., et al., *Liver Stiffness Measurement by Using Transient Elastography in Bangladeshi Patients with Type 2 Diabetes Mellitus and Ultrasonography-Diagnosed Nonalcoholic Fatty Liver Disease.* Diabetes Metab Syndr Obes, 2021. **14**: p. 3089-3096. 3. Hirooka, M., et al., *Validation of the FibroScan-aspartate aminotransferase score by vibration-controlled transient and B-mode ultrasound elastography.* Hepatol Res, 2021. **51**(6): p. 652-661. 4. Bafna, P., et al., *Prevalence of liver fibrosis by Fibroscan in patients on long-term methotrexate therapy for rheumatoid arthritis.* Clin Rheumatol, 2021. 5. European Association for the Study of the, L., et al., *Easl Clinical Practice Guidelines (Cpgs) On Non-Invasive Tests For Evaluation Of Liver Disease Severity And Prognosis- 2020 Update.* J Hepatol, 2021. [This expert also sent separately a copy of this publication: Jarvis H. et al. Engagement with community liver disease management across the UK: a cross-sectional survey.BJGPOpen 2021. DOI:10.3399/BJGPO.2021.0085]
		Expert #7	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0208798 https://bmjopen.bmj.com/content/9/5/e028591.abstract
		Expert #8	Very dynamic field and I cannot do this justice with selected publications
		Expert #9	UK evidence is from the scarred liver project ([redacted]). You will find in standard searches

20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1	(Not answered)
		Expert #2	Not that I am aware of
		Expert #3	No
		Expert #4	(Not answered)
		Expert #5	(Not answered)
		Expert #6	Litmus project: Testing Marker Utility in Steatohepatitis (LITMUS) funded by the European Innovative Medicines Initiative 2 Joint Undertaking, brings together clinicians and scientists from prominent academic centres across Europewith companies from the European Federation of Pharmaceutical Industries and Associations There are currently 165 clinical studies listed as recruiting subjects where Fibroscan is being utilised
		Expert #7	(Not answered)
		Expert #8	LiverScreen consortium (led by Barcelona) EU study ID-Liver Study (led by MAncheter and Nottingham) UK study
		Expert #9	The scarred liver project continues. NIHR RfPB study of using fibroscan to change behaviour in alcohol related liverdisease (KLIFAD). This is ongoing with results due end of 2021. I am chief investigator.

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1	Dependant on populations
		Expert #2	Many
		Expert #3	5% of the population
		Expert #4	if following NICE guidelines on screening for cirrhosis in hazardous drinkers with fibroscan then if all these patients were referred this would be 2 millon adults every 2 years. NAFLD - estimate about 20 % have NAFLD, 10% of these - so 2% of total adult population may risk of advanced disease so be eligible for Fibroscan - guidelines that this may need to be repeated every 3-5 years if riskfactors remain.
		Expert #5	IN SOUTHAMPTON ~400 A YEAR

		Expert #6	This will be dependant on approval and any restrictions – currently Fibroscan is within the NHS health check as anoption – it is rarely used due to limited access It was detailed in the 2020/2021 CQUIN for admissions for more than 24 hours to acute care directly pre pandemiclockdown – limited access makes biomarkers the differed option If only advocated for high-risk populations – T2DM, Dyslipidaemia, Hypertension Obesity, Viral Hepatitis, Alcohol thiswould still be a significant population Estimates suggest that 850,000 people are currently living with this condition who should all be offered a fibroscanFrom estimates in 2019 13.6 million people are at risk of T2DM >16 million individuals are suspected to have NAFLD COVID 19 severity and mortality has been linked to NAFLD with >10% liver fat by the UK Biobank The populations are large and increasing rapidly with obesity trends set to continue to rise, stratification of risk ispossible which reduces these to those at higher risk
		Expert #7	It would depend on the position in the pathway and the role of scanning in early diagnosis of fibrosis
		Expert #8	20-30 % of the population may have risk factors for CLD so potentially eligible
		Expert #9	There is information in the scarred liver project as to that a screening type approach based on diabetes and alcoholexcess codes in primary care can yield and the populations screened.

22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1	No
		Expert#2	Too many people to scan to make it available for all those who would be eligible
		Expert#3	No
		Expert #4	No
		Expert #5	IN PATIENT WITH VERY HIGH BMI, THIS PROCEDURE IS HARDER TO PERFORM
		Expert #6	Training, education and maintenance requirements – highly skilled and knowledgeable practitioners make this quickand accessible test easy to deliver The devices are mobile and easily transported from small cases suitable for public transport, taxi's to models which are large and require fixed locations
		Expert #7	(Not answered)
		Expert #8	Capacity of providing equipment and trained personnel
		Expert #9	No

23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert#1	No
		Expert#2	Cost of the equipment has been prohibitive
		Expert#3	No
		Expert #4	levels of knowledge/education amongst the primary care workforce on the indications and use of fibroscan are low. For adoption according to evidence based guidelines there needs to be education/? incentivisation for primary care asa majority are unaware of the indications for requesting fibroscan currently.
		Expert #5	COST OF HIRING/BUYING THE SCANNER CLINIC ROOMS AT GP PRACTICES
		Expert #6	Silo health management systems and the lack of awareness that poor liver health matters. The climate of inertia around assessing for or treating this chronic liver disease. Poor funding options and lack of awareness for the design and implementation of fibroscan services. Fibroscan exams are not for those with liver disease only, yet access is restricted by default to only these due to current pathways and specific guidance
		Expert #7	(Not answered)
		Expert #8	No
		Expert #9	No-inertia as usual plus lack of prioritisation of liver disease despite the huge burden of avoidable disease

24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Expert#1	Cost effective analysis
		Expert#2	Would this technology be better placed in the community before being referred to secondary care?
		Expert#3	No
		Expert #4	research into real world primary care implementation of liver pathways including fibroscan outside of the research environment
		Expert #5	None
		Expert #6	The assessment of patient v non-patient populations to identify the underlying level of poor liver health, awarenessand understanding.
		Expert #7	(Not answered)
		Expert #8	Research on serial change and behavioural change (post scan) will enhance its potential but there absence do notinhibit a current role
		Expert #9	KLIFAD study sets out to address potential harms-would a low fibroscan reading lead to increased alcohol consumption? There is a need for further studies in non standard NHS settings-alcohol services in community settings for example

25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: – Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these shouldbe measured. – Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert#1	Beneficial outcome measures: Yield of patients with F3/F4 fibrosis for secondary referralYield of F1/F2 patients not needing referral Yield of cirrhosis Cost benefit analysis Adverse outcome measures: Nil
		Expert#2	Beneficial outcome measures: Take up of the service and the percentage that show significant liver disease both in the GP setting AND if offered at Tesco as a random scan (the worried well) Adverse outcome measures: Patients falsely reassured that their lifestyle is not risking their health from a normal fibroscanPoor access to the technology from those who truly need advise Adverse mental health at being told they do have cirrhosis in the community setting without appropriate support to change
		Expert#3	Beneficial outcome measures: Reduction in number of cases referred to secondary care Identification of patients with advanced fibrosis Adverse outcome measures:

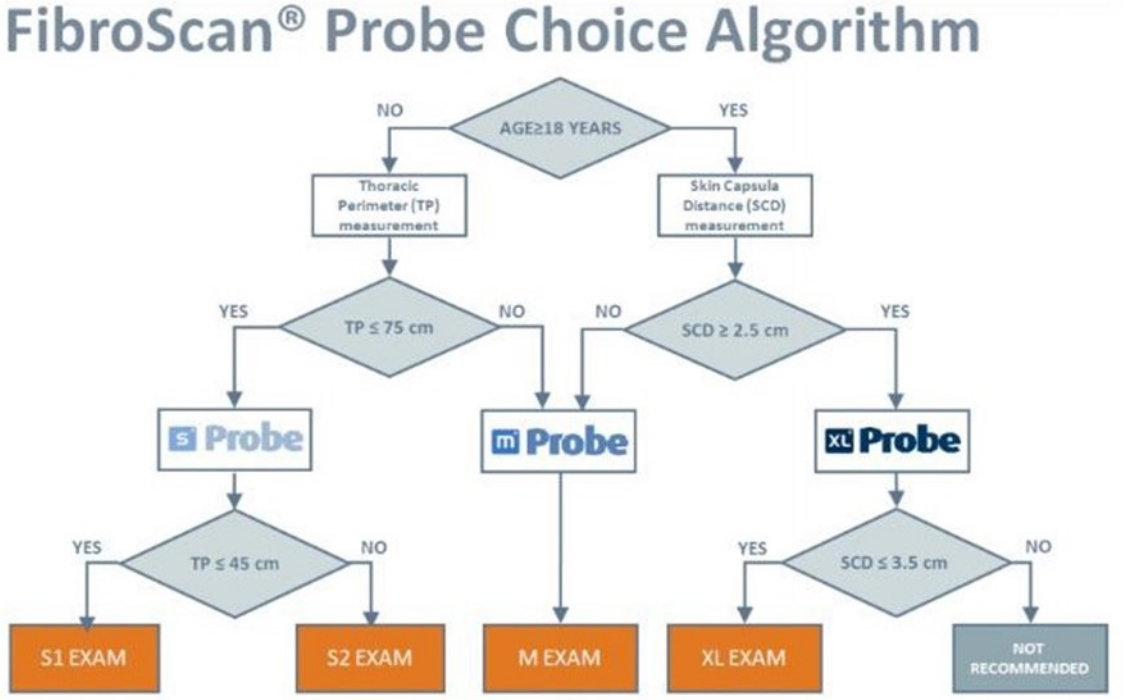
		Expert #4	Beneficial outcome measures: short term : number of new advanced fibrosis/cirrhosis cases detected per population v standard carenumber of appropriate v inappropriate referrals to secondary care number of referrals to secondary care long term - number of cases of decompensated cirrhosis admitted with no previous diagnosis of liver diseasemortality and morbidity from ARLD/NAFLD none relevant Adverse outcome measures:
		Expert #5	Beneficial outcome measures: EARLY DETECTION OF LIVER DISEASE/FIBROSIS IN ASYMPTOMATIC PATIENTS REDUCE PROGRESSION OF LIVER DISEASE BY MAKING PATIENTS WERE EARLIER REDUCE THE NEED TO SECONDARY CARE OUTPATIENT APPOINTMENTS Adverse outcome measures: NONE
		Expert #6	Beneficial outcome measures: Quality of life metrics in those who are located with poor liver health steatosis/fibrosis – Patient reported outcomes – several different validated options are available and may be used in disease specific areas Attendance rates, DNA rates Patient feedback and recommendations Fibroscan completion / failure rates – yearly figure IQR and accuracy for both CAP and KPa levels – yearly Number of fibroscans performed – age, sex ethnicity and condition Staff quality metrics for governance

			Current recommendations depend on fibrosis KPa levels and 3 – 5 yearly in many with low KPa but steatosis. Liver healthas demonstrated well by COVID-19 can alter rapidly with increased alcohol / high processed foods and more regular scanning may be required Implementation of lifestyle management plans in the USA with fibroscan and weight management use this every 3 monthto maintain and monitor outcomes Reduction in BMI, hypertension, lipid level and AST in associationImprovement of HBA1c and glycaemic control Maintained weight loss or improved diet quality in the absence of this Adverse outcome measures: Whilst there are no adverse outcomes from Fibroscan itself it can locate and risk stratify in association with other measurements those at highest risk of decompensation, such as Bavaeno criteria Adding Fibroscan to other measurements provides additional quality information which assists care and managementoptions
		Expert #7	(Not answered)
		Expert #8	Beneficial outcome measures: Diagnosis of advanced fibrosis/cirrhosis – multiple validated tools Diagnosis of significant fibrosis – validated thresholds Diagnosis of liver related outcome (decomspensation, HCC and death)- clinical registries Health economic outcomes Change in behaviour (alcohol and weight) Adverse outcome measures: Change in behaviour (alcohol and weight)
		Expert #9	Beneficial outcome measures: Diagnosis of significant liver fibrosis Prevention of admissions for decompensated cirrhosis Engagement with alcohol services Weight loss

			Adverse outcome measures: Increased alcohol consumption Failure to obtain readings

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology	Expert#1	(Not answered)
		Expert# 2	Those accessing the scans in hospital already are in the system. How do we capture the larger population, target the diabetics, obesity and harmful drinkers in the community. Make this technology more accessible to the general public aswell as the General Practitioner, district nurse, care home manager or pharmacist
		Expert#3	N/A
		Expert #4	(Not answered)
		Expert #5	(Not answered)
		Expert #6	We are the only provider of direct booking fibroscan in the UK to members of the public for health assessment and lifestyle. In my experience when people are exposed to fibroscan >90% have engaged positively in their lifestyle and liver awareness. They improve liver fat levels and recommend friends and family. There is increasing interest following COVID in those who have increased alcohol and dietary intake. Where quality of diet altered for the worse in some without reported weight gain there were increases in liver steatosis levels. Due to regularity of scans for some 3/12 inflammation was detectable to assist in primary care management – where a one-off scan would have indicated possible F3 fibrosis Improvement of liver education and awareness with fibroscan may assist in prevention of people developing liver diseaseand from becoming a patient. Fibroscan is a highly efficient and regarded non-invasive technology which has significant potential if available and delivered to primary care with knowledge and skill. Undiagnosed poor liver health had a significant impact in COVID-19 and fatty liver is the worlds biggest condition. Fibroscan is a leading locator and risk identifier with little current access.
		Expert #7	(Not answered)
		Expert #8	N/A
		Expert #9	(Not answered)

Appendix 2



In all cases, Echosens recommends taking 10 valid measurements.

Probe selection

UltraSound center frequency	Measurement depth (cm)	Criteria for use
5 MHz	S1 : 1.5-4 cm S2 : 2-5 cm	S1 : TP<45 cm S2 : 45<TP[1]<75 cm
3.5 MHz	M : 2.5-6.5 cm	SCD[2] < 2.5 cm
2.5 MHz	XL : 3.5-7.5 cm	2.5 <SCD< 3.5 cm

[1]: *Thoracic perimeter*; [2]: ***S**kin to **C**apsule **D**istance*

Appendix 3

Questions for Echosens (24/09/2021)

1) Our understanding is that Fibroscan first obtain its CE mark in 2003.
   When was it first launched in the UK?

2) Four versions of FibroScan are included in the clinical submission (630 Expert, 530 compact, 430 Mini+, 230 Go).
   a. Can you summarise the major differences between these versions?
   b. Thank you for the declaration of conformity for each of the four, can you please provide up to date CE certification for each also please?
   c. Thank you for the IFU for 630, 530 and 430. Can you please provide an IFU for the 230 Go version?

3) The bulk of primary care evidence uses FibroScan versions 402 and 502, can you please succinctly confirm the chain of equivalence from these to the 4 versions included in the clinical submission (FibroScan versions 630,530,430,230)? Nb. We have seen section 5.4 of the Clinical Evaluation Report (CER) for FibroScan with software v 4.1 under the MDR, but as the models within groups D01 and D02 are not defined, we are unable to track the claims of equivalence. In addition, there may have been further claims of equivalence to early models of Fibroscan for intermediate models in earlier CERs, which form part of the chain.

4) Are you aware of any diagnostic accuracy study which directly compares FibroScan used in a primary care setting to FibroScan used in a secondary care setting (with any model of device)?

Appendix 4

GID-MT562 FibroScan
Company Introduction meeting
05 October 2021 @ 11:00
[redacted]Joining Instructions: Zoom meeting

NOTES

Attendees:

Company (Echosens): [redacted]
Newcastle EAC: Andrew Sims (AJS), Kim Keltie (KK), Emma Belilios (EB)
NICE: Donna Barnes (DB), Thomas Walker (TW), Jacob Grant (JG)

1. **Welcome and introduction**

[redacted]- Global access and business intelligence manager, Echosens
DB - Project manager, NICE
JG - Technical lead, NICE
TW - Technical analyst, NICE
EB – comms lead, Newcastle EAC
AJS - Oversight, Newcastle EAC
KK – clinical lead, Newcastle EAC

2. **EAC questions – see Appendix**

An earlier version of the question list was shared with the Company on 24 September 2021, but no response was received. KK will send updated question list to the Company.

ACTION: KK to send updated question list to Company - COMPLETED 05/10/2021

[redacted] was able to respond to some of the questions verbally (responses added to Appendix), and will also provide full written responses. Deadline for written responses is close of business on **Friday 08 October**. [redacted] will share the written responses via NICE Docs.

ACTION: [redacted] to share written responses via NICE Docs by close of business Friday 08 October.

AJS thanked [redacted] for the inclusion of the Clinical Evaluation Report with the clinical evidence submission. He asked if [redacted] could provide a written definition of the differences between D01 (new generation) and D02 (former generation) devices.

ACTION: [redacted] to provide written summary of differences between D01 and D02 devices in the clinical evaluation report

3. **Company questions**

[redacted] confirmed he is clear on the process and the information he needs to provide by the end of the week.

4. **Confidentiality and the Correspondence Log**

NB: Further to this meeting, the EAC will communicate directly with the Company (and vice versa), copying NICE in. All correspondence should be via email. ***All correspondence that informs the assessment will be published in the correspondence log on NICE's website as supporting information when the final guidance is published****. It is the Company's responsibility to highlight for redaction any information that is commercially sensitive ([redacted]) or academic in confidence ([redacted]).*

5. **Next steps**

Economic submission 19/10/2021 - [redacted] confirmed this is on target.
Company engagement call 27/10/2021
Final report due from EAC on 16/11/2021

6. **AOB**

There was no other business

Appendix - EAC Questions for Company

Questions for Echosens (24/09/2021)

1) Our understanding is that Fibroscan first obtain its CE mark in 2003.
   When was it first launched in the UK?

   Response: First device sold in the UK in 2005

2) Four versions of FibroScan are included in the clinical submission (630 Expert, 530 compact, 430 Mini+, 230 Go).
   a. Is 630 PRIME included also (can also be used to scan liver)?
      (IFU lists 630)
      Response: 630 PRIME - measures spleen stiffness, out of scope for this topic, but also measures liver stiffness as well.
   b. Can you summarise the major differences between these versions?

	430 Mini+	530 Compact	630 Expert	230 Go	502 (not sold anymore)	402 ((not sold anymore)
LSM by VCTE	Yes	Yes	Yes	Yes	Yes	Yes
CAP	Yes	Yes	Yes	Yes	Yes	No
SSM by VCTE	No	No	Yes	No	No	No
FibroScan Gateway compatibility	Yes	Yes	Yes	Yes	No	No
MyFibroScan compatibility	Yes	Yes	Yes	Yes		No
Embedded ultrasound localization system for assessment of obese or complex patients	No	No	Yes	No	No	No
Fully transportable	Yes	No (but can be used with a cart)	No	Yes	No	Yes
Battery-powered	Yes	Yes	No	No	No	No
Weight	5kg	10kg	46kg	5kg	41kg	8kg
Screen	Dedicated computer within device	Dedicated computer within device	Dedicated computer within device	Separate computer required (with internet	Dedicated computer within device	Dedicated computer within device

				access for user authentication and with FibroScan software installed		

c. Thank you for the declaration of conformity for each of the four, can you please provide up to date CE certification for each also please? **Provided – thank you**
d. Thank you for the IFU for 630, 530 and 430. Can you please provide an IFU for the 230 Go version? **Provided – thank you**
e. <u>230 Go:</u>
    i. is a computer required during use (or it is just to download output after use)? **Response**: User will require PC/laptop
    ii. IFU mentions “Cloud”. Can you let us know the purpose of the cloud?
    iii. Terminology check: S+, M+, XL+ probes, conduct S1, S2, M, XL exams? **Response:** Correct
    iv. All FibroScan systems can use the 3 probes? **Response:** Yes. Clinician would start with the medium probe. If the distance between the skin and the liver is too great, the device will prompt use of XL probe (higher shear wave). If distance is too small, device will prompt use of S probe. Top of probe is bigger for XL, smaller for S probe.
    v. Cost perspective: Are S+, M+ and XL+ probes purchased separately from the FibroScan system? Are each purchased individually or as a bundle? **Response**: M+ probes provided with capital purchase of FibroScan 630/530/430, S and XL probes to be purchased separately.
    vi. Cost perspective: what is the average lifespan of a probe? **Response**: Seven years

3) The bulk of primary care evidence uses FibroScan versions 402 and 502, can you please succinctly confirm the chain of equivalence from these to the 4 versions included in the clinical submission (FibroScan versions 630,530,430,230)? Nb. We have seen section 5.4 of the Clinical Evaluation Report (CER) for FibroScan with software v 4.1 under the MDR, but as the models within groups D01 and D02 are not defined, we are unable to track the claims of equivalence. In addition, there may have been further claims of equivalence to

early models of Fibroscan for intermediate models in earlier CERs, which form part of the chain.

Response:

[redacted]

- Are 402/502 portable or cart based? **See Table above**
- What weight are 402/502? **See Table above**
- Do they have a dedicated screen (or separate computer required)? **See Table above**

Response: [redacted] has shared with a colleague who will provide a summary by the end of the week. He will add the additional 2 versions (FibroScan 502, 402 to the above table).

4) Controlled Attenuation Parameter – it is stated in the submission that CAP is option when using FibroScan (is this applicable to 630,530,430,230,502 and 402 versions). Does this require a software upgrade to do this? Terminology check: any FibroScan system can conduct this measurement, however as per IFU only the M+ and XL+ probes can take this measurement (is this correct)?
   Response: Yes, CAP is possible for all versions with the exception of 402 and 502 versions as these are no longer available.

5) However is SmartExam (continuous CAP measurement) also an option across all versions of FibroScan (newer and older generations)? Again is it a software upgrade that enables this across all versions (630,530,430,230,502 and 402 versions)? Again only possible in M+ and XL+ probes?
   Response: Yes (same as above).

6) In line with the final scope, are you aware of any diagnostic accuracy study which directly compares FibroScan used in a primary care setting to FibroScan used in a secondary care setting (with any model of device)?

   Response: None were identified during the literature review

   AJS clarified that the kind of study the EAC is looking for, patients would be scanned in a primary care setting, then referred into secondary care and re-scanned (paired analysis).
   Response: Will respond by the end of the week. Need input from the medical team.

Economics:

Could you give us any information regarding the economic model, in terms of:

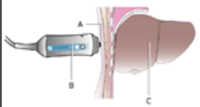
- Software used (Excel, other)
- Model structure (cost calculator, decision tree, Markov)

Approach taken given lack of comparator information?

Response: Model will be a simple cost consequences model, built in Excel, using template provided by NICE. [redacted] is meeting the team developing the model later today.

Appendix 5

	Comparison items for liver examination		Fibroscan 502 Touch	Fibroscan 502	Fibroscan 402	Fibroscan 430 Compact	Fibroscan 430 Mini / Mini+	Fibroscan 630	Fibroscan 230	Difference
TECHNICAL EQUIVALENCE	*Principle	Work Principle	[illegible]	identical	identical	identical	identical	identical	identical	No difference
		Functional Mechanism	[illegible]	Identical except the second generation CAP (CAPc) is not available on the product.	Identical except the CAP (first and second generation) is not available on the product.	identical	identical	identical	identical	[illegible]
	*Structure and Components	[redacted]								
		Core Component	Elastography engine (PV2)	Elastography engine (PV2)	Elastography engine (PV2)	Elastography engine (PV4)	Elastography engine (PV4)	Elastography engine (PV4)	PV4_Software (PV4)	[illegible]
	*Software System		Software version CUPC 4.1	CUPC A2.2	CUPC 6.21	Software version CUPC 4.1	Software version CUPC 4.1	Software version CUPC 4.1	[illegible]	Refer to software release letters.
	*Performance specifications		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[redacted]									

CLINICAL EQUIVALENCE		Applicable Part of Human Body	Liver	Identical	Identical	Identical	Identical	Identical	Identical	No difference
		Way to Contact Human Body	The ultrasound transducer of the probe is a "type BF applied part", and is the only component of the FibroScan unit in contact with the patient. As soon as the button is pressed (if sufficient force is placed on the transducer), the electrodynamic transducer generates a shear wave (vibration) that painlessly impacts the patient's skin. At the same time, the ultrasound transducer performs a series of acquisitions (emission/reception) to measure the propagation speed of the shear wave. Acquisition lasts less than one tenth of a second.  ***How to use a probe: A:** Ultrasound transducer. **B:** Electrodynamic transducer. **C:** Liver*	Identical	Identical	Identical	Identical	Identical	Identical	No difference
		Intended Use	The FibroScan® device is intended to provide: • liver stiffness at 50Hz shear wave frequency, • liver ultrasonic attenuation (CAP) at 3.5 MHz.	Identical except that second generation CAP (CAPC) is not available on the product.	Identical except that CAP (first and second generation) is not available on the product.	Identical	Identical	Identical	Identical	First generation CAP is available on FibroScan 502, FibroScan 502 Touch, FibroScan 630 Compact, FibroScan 430 Mini / Mini+, FibroScan 630, FibroScan 230. Second generation CAP (CAPC) is available on FibroScan 502 Touch, FibroScan 630 Compact, FibroScan 430 Mini / Mini+, FibroScan 630, FibroScan 230.
		Indications for use	Liver stiffness and CAP are indicated as an aid to diagnosis and monitoring for adult and pediatric patients as part of an overall assessment of liver disease.	Identical except that second generation CAP (CAPC) is not available on the product.	Identical except that CAP (first and second generation) is not available on the product.	Identical	Identical	Identical	Identical	First generation CAP is available on FibroScan 502, FibroScan 502 Touch, FibroScan 630 Compact, FibroScan 430 Mini / Mini+, FibroScan 630, FibroScan 230. Second generation CAP (CAPC) is available on FibroScan 502 Touch, FibroScan 630 Compact, FibroScan 430 Mini / Mini+, FibroScan 630, FibroScan 230.
		Target Population	The FibroScan® device is intended to be used on pediatric and adult patients.	Identical	Identical except pediatrics (no S+ probe for FS 402)	Identical	Identical	Identical	Identical	The S+ probe is not available with FibroScan 402.
		Intended Environment	This device is intended to be used in hospitals, clinics or any other healthcare facility.	Identical	Identical	Identical	Identical	Identical	Identical	No difference
		Intended User	Use of the device The FibroScan® device is intended to be operated by clinical staff. No specific knowledge or experience in the operation of ultrasound imaging devices is required. The FibroScan® device shall be operated only by people trained and certified by Echosens or its local representatives. Interpretation of the results The measurements obtained by operating the device are intended to be interpreted by a physician experienced in dealing with liver disease.	Identical	Identical	Identical	Identical	Identical	Identical	No difference
	Use Method		The FibroScan and its probes make up an active, non-implantable medical device using ultrasound.	Identical	Identical	Identical	Identical	Identical	Identical	No difference
	Precautions		The FibroScan device must be used with the following precautions of use: • Probe and/or measurement type shall be selected according to the recommendations described in the examination procedure chapter. • It is recommended not to trigger the measurement when the device displays the alert "Liver too deep". In such case, operator may change probe and/or measurement point. • Presence of ascites between the probe and the liver may prevent measurements from being obtained. • Patient shall be fasting for 3 hours or more.	Identical except that the alert "Liver too deep" is not available on this product.	Identical except that the alert "Liver too deep" is not available on the product.	Identical	Identical	Identical	Identical	No difference
	Contraindication		The FibroScan® device must not be used in the following situations, to ensure patient safety: - On an organ other than the liver, - On eyes and mucosa, - On wounds. The S+ probe is not validated for patients under 14 years of age.	Identical	Identical except that the FibroScan 402 must not be used in the following situations: - On patients less than 14 years old (no S+ probe) - On patients with a thoracic perimeter of less than 75 cm (no S+ probe)	Identical	Identical	Identical	Identical	No difference
BIOLOGICAL EQUIVALENCE	Parts in contact with patient body		The device consists of a main unit and probes. The main unit is a casing containing electronic circuits, personal computer and power supply unit. The probe consists of a multi-sonic transducer mounted on the axis of a vibrator. The vibrator and associated embedded electronics are enclosed inside a casing. The ultrasonic transducer is the only element which protrudes outside of the probe casing. The probe is connected to the main unit by a cable. In normal conditions of use, only the ultrasound transducer, more especially the active surface of the ultrasonic transducer and its casing, and possibly the membrane surrounding the transducer enter into contact with patients' skin.	Identical	Identical	Identical	Identical	Identical	Identical	No difference. Same probes are used.
	Biological safety		Materials in contact with patient body	Identical	Identical	Identical	Identical	Identical	Identical	No difference. Same probes are used.

Component	Material	Color	Nature of body contact
Transducer			
- Active part	Hard lens polyurethane (reference HFPU P100)	Grey	In contact with healthy skin
- Casing	Plastic material (reference UL L100)	Black	In contact with healthy skin
Membrane	Silicon material (MED-4050 / CH-007 Or Silicone White HDDIX 7329	White	In contact with healthy skin
Glue (to assembly the membrane and the diffuser that is not in contact with patient	Loctite 4061 Loctite 7701 (primer)	Transparent	Potentially in contact with healthy skin
Glue (to assembly membrane and transducer)	Teroson® Terostat™-9140	Transparent	Potentially in contact with healthy skin

Appendix 6

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

• Expert Engagement Meeting

FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care [MT562]

Date: **Wednesday 13 October 2021**
Time: **14:00 – 16:00**

Documents

MIB: **https://www.nice.org.uk/advice/mib216**

MTG Scope: **https://www.nice.org.uk/guidance/gid-mt562/documents/final-scope**

In Attendance:
NICE: Donna Barnes (DB), Thomas Walker (TW), Jacob Grant (JG), Tara Chernick (TC) - Health Technology Adoption Manager, Alex Sexton (AS)

Newcastle EAC: Andrew Sims (AJS), Kim Keltie (KK), Emma Belilios (EB)

DAC Chair: Dr Mark Kroese (MK)

Experts:
- Louise Campbell - Clinical Director, Tawazun Health (a CQC regulated FibroScan Service provider)
- Prof Neil Guha - Professor of Hepatology, University of Nottingham
- Dr Coral Hollywood - Consultant hepatologist, Gloucestershire Hospitals NHS Foundation Trust
- Dr Helen Jarvis - GP Partner, NIHR clinical doctoral research fellow, Newcastle University
- Dr Deepak Joshi - Consultant Hepatologist, King's College Hospital, NHS Foundation Trust
- Prof Michael Moore - Professor of Primary Care Research, University of Southampton
- Dr Janisha Patel - Consultant Hepatologist, University Hospital Southampton
- Dr Stephen Ryder - Consultant physician in hepatology and gastroenterology, Queens Medical Centre, Nottingham

NOTES

1. **Welcome and introductions**
   Confidentiality documents signed in advance.

2. **Questions for the professional experts (see below)**

   Responses to questions

3. **Next steps**

   - EAC will submit the final Assessment Report 16/11/2021
   - Draft guidance Committee meeting 19/01/2022
   - Public consultation 09/02/2022 - 09/03/2022
   - Final guidance Committee meeting 22/03/2022
   - Publication May 2022

Questions for discussion

- **What is the current practice for screening patients at risk of liver fibrosis or cirrhosis?**
  The experts agreed there is no consistent screening approach nationally. Local practice variations include screening using FibroScan in primary care, screening using Enhanced Liver Fibrosis (ELF) blood tests in primary care, and referrals to secondary care for screening in high risk groups. High risk groups include patients diagnosed with non-alcoholic fatty liver disease (NAFLD) and patients with alcohol related liver disease (ALD). Patients may have their risk of fibrosis assessed using the FIB-4 risk calculator or NAFLD Fibrosis Score (NFS). FIB-4/NFS calculate risk score from blood test results and other clinical information. Patients identified as being at higher risk may then be screened using FibroScan if available, however FibroScan isn't available in all regions.

  A national survey of community liver disease management carried out on behalf of the British Liver Trust (Jarvis *et al*. 2021) suggested that in the UK around 25% of CCGs have access to FibroScan.

  Where FibroScan is available in primary care, local pathways differ. One expert reported that it had taken four years to get a FibroScan pathway established in their area. FibroScan would be part of a referral pathway rather than a standalone test. Primary care networks (PCNs), part of the NHS long term plan, may invest in FibroScan, leading to greater homogeneity in the future.

  One expert commented that the quality of FibroScan machines available in primary care/community settings is variable. Around 1/3 of devices in community practices are older devices which cannot be upgraded and don't have controlled attenuation parameter (CAP) capability. One expert (secondary care) reported that their Trust uses a 'pay per scan' model, so it's the Company's responsibility to maintain/upgrade devices.

  TW asked if British Society of Gastroenterology (BSG) guidance informed pathways. Experts responded that BSG guidelines are a signpost rather than a 'must do'. There are clusters of disease nationally, so varying levels of demand, and overlapping guidelines (BSG, NICE). The issue is not just how to deal with abnormalities detected, but also, the underlying risk factors (obesity, excessive alcohol consumption). Guidelines are brought together in local protocols with a lot of regional variation.

- **Are there established thresholds based on transient elastography scores that are used to make decisions in the NHS?**
  There is an established threshold for cirrhosis (15kPa). There was general consensus that applying a threshold of 8kPa for referral would mean the chances of missing advanced disease are minimal. A few patients with scores below 8kPa but high CAP scores and additional risk factors may still need to be referred. One expert suggested

that from a primary care perspective, using a lower threshold is helpful to safely rule out advanced disease. In secondary care thresholds may be used differently. The experts acknowledged that thresholds for intermediate stages of fibrosis have been proposed but that there is less evidence for their use.

One expert reported that their service had initially set a threshold of 8kPa but were overwhelmed by demand, so moved the threshold to 10kPa. High risk patients who are not referred will be monitored every 3 years. Currently they are seeing about 600 patients a year, of which 400 require repeat assessment and the rest are referred back into the primary care pathway (or come off the pathway if their score is below 6kPa).

- **If used outside secondary or specialist care (for example in primary care), what member of staff would conduct the FibroScan measurement? How long (minutes) does it take to conduct 10 measurements?**

  The experts agreed anyone can be trained to use FibroScan. It usually takes between 10 and 15 minutes to conduct 10 measurements, although two experts commented that this could be longer depending on patient's body habitus and whether you need to change probes.

  One expert commented that if an unqualified practitioner conducts the scan, there may need to be a separate appointment for the GP to discuss the results with the patient. This is more time consuming (and the patient may not attend, so will lose the opportunity to discuss the implications of the result). A skilled nurse practitioner conducting the TE measurement can discuss the results with the patient at the time, which may remove an appointment from the timeline. Some centres use a mix of pathways, including virtual consultations.

  One expert mentioned the additional functionality from optional software enhancements, e.g. Smart Exam.

- **What is the likely impact on the NHS to start using FibroScan outside secondary or specialist care? For example, need for re-design of local pathways, need for training of further staff to use the device etc**.
  FibroScan devices will need servicing and maintaining. The overall impact will depend on the original local pathway. Thresholds will vary depending on whether Centres are using the test as rule-in or rule out. Interventions for liver fibrosis would usually be lifestyle counselling (as alcohol abuse or obesity are the main causes). As well as costs, need to consider benefits from earlier identification.

  One expert moved from developing and delivering a large NHS FibroScan service to a dedicated private service. The dedicated service can take advantage of economies of scale that are not possible within the NHS currently. They suggested that different models should be considered to meet the demand.

- **Is FibroScan used in primary care as a triage for referrals for measurement in secondary care? Or would it replace secondary care measurement? Would secondary care physicians act on the results of a FibroScan done in primary**

care, or would they repeat the test?

One expert (secondary care) confirmed that they would not repeat the FibroScan measurement that prompted the referral. They noted that the patients referred to them will have had their FibroScan performed by a very competent hepatology nurse (lucky to have this specialism). Once the patient is in the secondary care system, they will typically receive a brief intervention, then be re-assessed. The interval of reassessment being guided by transient elastography measurement (high measurement, more frequent assessment).

One expert commented that in their region they are looking at setting up a community diagnostic hub, which will include FibroScan. They did not anticipate that patients referred into secondary care in this way would require a repeat scan in secondary care.

Most patients will initially be identified through a blood test showing abnormal liver biomarkers. Consensus was that a FibroScan in primary care would be a viable alternative to FibroScan in secondary care, although one expert suggested a risk based approach. Need for risk based management: people at higher risk of severe disease should have more intense assessment, people at low risk can be assessed in the community.

- **Do you think there is likely to be any change in the number of people who attend their FibroScan appointments in primary care compared to secondary care?**

  One expert reported that data from a pilot study they were involved with suggested a 'did not attend' (DNA) rate of 40% in secondary care, falling to 10% in primary care. They suggested this was largely due to convenience.

  ACTION: NG to share reference to pilot study which reported drop in DNA.

  Primary care locations tend to be closer for patients, and there are less issues with parking costs etc. Another expert agreed, community DNA rates are lower.

  One expert noted that 'primary care' is a broad concept which can include community hubs, PCNs. Important to consider optimum placement of diagnostics to benefit from economies of scale without compromising accessibility.

  One expert commented that DNA rates differed depending on the reason for the scan. They see higher attendance rates for appointments following abnormal test results compared with routine screening appointments.

- **Is either the accuracy of the FibroScan or the likelihood of the test not working likely to depend on the experience of the person doing the test? Would the setting (e.g. a community nurse using a portable version in a care home, versus a practice nurse using a device in a GP clinic room) affect the accuracy?**

  One expert commented that FibroScan is a very quick process to learn, and users become proficient very quickly, especially if they are running a dedicated clinic.

However, experts did accept there's a failure rate. For larger patients, need an XL probe and the scan is more difficult to do, so do need an alternative (usually, blood test) for patients where you can't get a good quality scan. Failure rate is higher during the learning process, even though it is quick to become proficient.

The experts did not think that the location of the FibroScan measurement would affect accuracy. One expert commented that practitioners do need to look at the elastogram rather than just the score. If the elastogram is wrong the score will be inaccurate.

- **What is the test/retest reliability of FibroScan when it is used in primary and community care?**

  AJS asked, particularly, were the experts aware of any published studies looking at the reproducibility of the FibroScan score in primary care repeated in secondary care.

  LC confirmed there are studies showing re-test reliability. Where the user is well trained, correlation is good. LC will forward the references.

  ACTION: LC to forward references to studies showing test/retest reliability - COMPLETED, four studies supplied 15/10/2021:Recio *et al*. 2013, Neukam *et al*. 2009, Perazzo *et al*. 2015, Fraquelli *et al*. 2007

- **What is the impact of a false negative (has fibrosis/cirrhosis and does not have it detected using FibroScan in primary care)? Are patients at risk of fibrosis/cirrhosis reviewed annually?**

  One expert estimated that about 50% of cirrhosis cases are identified through events. There are implications for missing cirrhosis. If the result is very far out the risks are greater. Repeat testing for high risk patients would minimize the risk.

  MM will share long-term follow-up paper on repeat testing. There is no doubt that liver fibrosis is a progressive disease.

  ACTION: MM to share long term follow up paper on repeat testing (EAC query: is this the Reinson et al. 2021 paper?).

  The experts agreed that the ideal screening interval is not known currently. Guidance varies between one, three and five years. Most of the experts retest at three year intervals (pragmatic, from cirrhosis progression modelling). One expert commented that an interval of three years gives people a reasonable time frame to make lifestyle changes and give the liver time to repair.

  Stiffness is a physiological measurement. There is no perfect biomarker for advanced fibrosis, but there is a good correlation between liver stiffness and level of fibrosis, and the experts agreed FibroScan has a high negative predictive value. One expert estimated that using a cut-off value of 15, sensitivity for cirrhosis was around 70%. Re-testing patients is a good safety net.

One expert suggested that if a patient is identified as having lots of risk factors they should probably be re-tested more frequently. Another expert commented that these higher risk patients would usually have other conditions as well, which would be monitored regularly, for example annual diabetes review, hypertension, so their risk assessment can be adjusted dynamically.

- **What is the impact of a false positive (patient has elevated transient elastography via FibroScan in primary care but does not have fibrosis/cirrhosis)? Would these patients all be sent to secondary care for confirmation? Would these patients all be sent for biopsy confirmation?**

  One expert commented that we don't know true false positive/negative rates. The best data available currently is probably Thiele *et al.* 2018 (study from Denmark with large biopsy rate).

  Experts thought that high risk group would probably be sent for biopsy confirmation, for intermediate risk group there would usually be a discussion about the pros and cons of proceeding to further investigation.

  One expert commented that if further investigations revealed the patient did not have fibrosis/cirrhosis, it would be reassuring for the patient to know they had been investigated thoroughly and did not have the condition. This would be a better scenario than not carrying out further investigations in a patient because they had a false negative result.

  Another expert commented that false reassurances (from a false negative result) could encourage negative behaviour (as patient may interpret this as, they actually don't need to lose weight, reduce alcohol intake).

  The experts agreed that the lifestyle interventions that would be recommended if a patient received a false positive result (to support weight loss or reduce drinking) are not harmful (in fact, likely to be beneficial in any case for patients at risk of fibrosis) so no danger of harm caused through inappropriate treatment. Avoidable biopsy may be a consequence of a false positive.

- **What are the complications of biopsy? What proportion of biopsies experience complication?**

  One of the experts confirmed there is good evidence to show that liver biopsy is safe. They referenced a key paper (Joe West and Timothy R.Card, 2010), which shows major bleeding rates of 6 in 1,000, and mortality rates of 1 in 10,000).

- **Would transient elastography in primary care screening be repeated (for patients deemed at risk)?**

  Dealt with previously.

- **Any other comments?**

  One expert commented that as well as variable availability in primary care, there are still some hospitals that don't have FibroScan at all, also some have older machines that need updating.

One expert noted that new guidelines published a few days ago (EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update) recommends FibroScan for risk stratification in patients with NAFLD and ALD. There is a momentum to improve access across the UK, and to broaden the range who consider liver health as part of the integrated care pathway.

Appendix 7

Clinical queries (sent 25/10/2021 to 9 clinical experts, 6 responses received)

Expert No.	Name
#1	**Dr Janisha Patel**
#2	**Dr Deepak Joshi**
#3	**Louise Campbell**
#4	**Prof Neil Guha**
#5	**Dr Stephen Ryder**
#6	**Dr Ashis Mukhopadhya**
#7	**Dr Coral Hollywood**

1. The company's economic model starts with people having been identified as intermediate or high risk, by FIB-4. This appears broadly in line with BSG guidelines for NAFLD.
    a. However, studies have shown that FIB-4 is a poor predictor of fibrosis, and NICE guidance relating to NAFLD, ARLD and cirrhosis does not mention use of FIB-4. Therefore is the company entry point valid? Is it valid for NAFLD, ARLD and hepatitis? How else would "at risk" patients be identified, and would clearer guidance on indications for using FibroScan be useful?
    b. Assuming intermediate FIB-4 (1.30-3.25 using BSG guideline for NAFLD) is an appropriate indication for FibroScan, approximately what proportion of "at risk" patients would have FIB-4 within this range (1.30-3.25)? Can you estimate the proportion with liver disease that could be missed, with FIB-4 outside of the at risk range?

Responses

#1	a. In Hampshire, Southampton and IOW – we are using ELF as per the NICE 2016 NAFLD guidelines. We also use ELF to screen Arld. Entry point of community fibroscan service is ELF>9.5. There should be some biological mark to enter the fibroscan service to avoid inundating the fibroscan service. b. Simple and Clearer guidance on indications for Fibroscan will be useful for GPs
#2	Did not answer this question
#3	NICE guidance for NAFLD (2015) requires updating and does not reflect the addition of CAP to Fibroscan. ELF which was advocated as choice and was and remains sparsely used in many areas either in the UK or elsewhere. Recent publications by APASL, EASL NIT guidelines and the most recent AGA clinical pathway publication for NAFLD risk suggest and evidence FIB-4 followed by sequential FibroScan above 1.3 and below 2.67. The number they would suggest as required in this indeterminate zone is 30-40% within the high-risk populations with T2DM, 2 or more Metabolic risks and incidental findings of abn LFT or fat on screening modality. Fib-4 <1.3 or < 2.0 in those over 65 has a negative predictive factor of ≥ 90% in NAFLD making it a good, inexpensive test for primary care

	The EASL NIT guidelines demonstrate good and recent (2021) guidance on FibroScan in various liver disease and cirrhosis with Baveno, Enhanced Baveno and FAST score systems – these have yet to be reflected din BSG, NICE guidelines A FIB-4 >2.67 has a high risk for advanced fibrosis = positive predictive factor of 60%-80% SAME AS ABOVE - Recent publications by APASL, EASL NIT guidelines and the most recent AGA clinical pathway publication for NAFLD risk suggest and evidence FIB-4 followed by sequential FibroScan above 1.3 and below 2.67. This maximises the opportunity to include most people at risk who present to a primary care area and tested The number they would suggest as required in this indeterminate zone is 30-40% within the high-risk populations with T2DM, 2 or more Metabolic risks and incidental findings of abn LFT or fat on screening modality. Fib-4 <1.3 or < 2.0 in those over 65 has a negative predictive factor of ≥ 90% in NAFLD making it a good, inexpensive test for primary care
#4	a. This is a really important point. Many guidelines use FIB-4 as an initial "triage" test to reduce further downstream fibrosis tests. There is emerging evidence (including our work: Chalmers J, Wilkes E, Harris R, Kent L, Kinra S, Aithal GP, Holmes M, Johnson J, Morling JR, Guha IN. The Development and Implementation of a Commissioned Pathway for the Identification and Stratification of Liver Disease in the Community. Frontline Gastroenterol. 2020 Feb 10;11(2):86-92. doi: 10.1136/flgastro-2019-101177. Epub 2019 Jun 26. PMID: 32066993; PMCID: PMC7025872) that FIB4 can miss disease. The advantage of this approach is that it reduces downstream tests and investigations esp if abnormal ALT is used as the starting point (e.g. Camden and Islington pathway Srivastava A, Gailer R, Tanwar S, Trembling P, Parkes J, Rodger A, Suri D, Thorburn D, Sennett K, Morgan S, Tsochatzis EA, Rosenberg W. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. J Hepatol. 2019 Aug;71(2):371-378. doi: 10.1016/j.jhep.2019.03.033. Epub 2019 Apr 6. PMID: 30965069.) Another way to define risk would be to look at risk factors (RFs) : excess alcohol consumption, type 2 diabetes , obesity) But this is not universally agreed by the community or society guidelines… although the NICE guidance does allude to this approach for alcohol and NAFLD. The reluctance to go down this road is related to perceived numbers as 10-30 % of population may have at least one of these RFs. b. Some data on this form the 2 studies mentioned above. The problem with the miss rate is data is extrapolated from secondary care and the spectrum bias in primary care may be different
#5	a. FIB4 is used as a rule out test, ie a low value is useful and stops further tests. It is proven for NAFLD and Hepatitis, the data on alcohol is more variable but overall probably still holds true. The best data for NAFLD is William Rosenberg's north London ELF pathway (I view ELF and

	fibroscan as totally equivalent) and this gives cut offs and the proportion with intermediate values for FIB$ I NAFLD (see below). b. I cant recall exact numbers but its tiny and not a clinical worry at all.
#6	a. Fib 4 scores have had better sensitivity and specificity than other non-invasive markers and has been studied in NAFLD. b. The cut off values of < 1.30 actually separates out patients with low risk (not no risk). All these patients have fatty liver and there is a premise to repeat these values in 2-3 years' time as they are still at a theoretical risk of progressing. From the Camden pathway, this group with low risk was around 70% of the entire cohort.
#7	a. Fib 4 is good for deciding on no fibrosis or at the other end of the spectrum when scarring is severe, it is not very good in the interderminate range. We can consolidate with a fibroscan and see if this gives any more info. The other way is to do an ELF for indeterminate scores, but this is expensive and many trusts do not fund it. b. I think you would need a statistician for this or someone who has done an indepth study of the epidemiology of liver fibrosis

2. The company's model assumes that the "test failure" rate is equal in primary and secondary care. If we assume that the same devices and probes are available in both settings, is this assumption valid or would you expect a difference in test failures between primary and secondary care?

Responses

#1	The failure to achieve Fibroscan reading is body habitus most often. In secondary care we can offer US elastography in though that have failed fibroscan in the community. This is not a portable machine therefore easy of use in the community Fibroscan is helpful. If they have failed with Fibroscan in the community there is little gain to repeat the same scanning technique in secondary care
#2	This will depend on the operator. If the operator is correctly trained then the test failure rate should be the same.
#3	I would expect and in personal experience NO difference in the success / failure rates where the person performing the scan is experienced and regularly scans We cannot assume that the equipment is the same as there is disparity throughout the NHS on models, age and software available – this poses a risk to the results – NOT all devices have CAP capability – which should be an essential requirement to all models used in primary care
#4	I think this is valid – equipment should be the same in primary and secondary care.
#5	It is valid. Good evidence from Prof Guha's community fibroscan data that the failure rate is low.
#6	The positive predictive value of any test depends on the prevalence of the disease. In the unselected larger cohort in primary care the prevalence will be lower than the selected group of liver patients coming to secondary care in hospital. So just on this basis the test failure would be higher in primary care.
#7	The training should all be the same, though a different scanner on a different day may be able to gain a reading on a patient that was a test failure the day before. The rate of test failures would be expected to be the same whether in primary or secondary care

3. The economic model assumes that patients for whom a result is not produced, will not go on for further testing or follow-up and will either have no liver disease, or undiagnosed and untreated liver disease, in the same way as if they had not attended the scan at all. Is this a reasonable

assumption? If not is it reasonable to assume that all patients with failed test in primary care would be referred to secondary care for another FibroScan assessment or other investigations? What would these be and in what proportions?

Responses

#1	In our experience proportion who have failed primary care fibroscan is 1-2%. They are referred to secondary care for a US elastography. Only if this fails then we review the patient in hepatology clinic to assess the risk and need for surveillance for HCC.
#2	I think that all patients with a failed test will be referred into secondary care.
#3	The reason for failure needs to be ascertained and corrected where possible to ensure true failure – fasting, body habitus….other scan staff may be utilised All patients with another modality indicating a positive result to indicate a risk of liver fibrosis should be sent to a specialist unit for further assessment Reassessment may be required as a follow up defined by the physician on discussion.
#4	I agree a scan failure will either need another fibrosis test (e.g. ELF blood test) or referral to secondary care
#5	This isn't right. If fibroscan fails you will need another form of assessment, this can be ELF testing or in a proportion liver biopsy (this will depend on other clinical factors which may suggest advanced fibrosis). I would think that the majority would have ELF testing (90%).
#6	The BSG guidelines and other guidelines are not definitive but suggests monitoring the low risk group every 2-3 years. As alluded earlier the natural history of the disease means that these patients do need follow up in primary care.
#7	*The economic model assumes that patients for whom a result is not produced, will not go on for further testing or follow-up and will either have no liver disease, or undiagnosed and untreated liver disease, in the same way as if they had not attended the scan at all. Is this a reasonable assumption?* This will depend on the referral pathway. GP's in my trust can refer directly for fibrscan if they do not attend the hepatology service will not be involved. If referred from hepatology it will have been from a clinic and the patient will still be in the system. *If not is it reasonable to assume that all patients with failed test in primary care would be referred to secondary care for another FibroScan assessment or other investigations*? This will be done to the referral pathway and whether these patients are captured. What would these be and in what proportions? I am not sure of the amount of DNA's from STT referrals from primary care

4. The company's model assumes three possible outcomes following FibroScan:
    - No behavioural intervention
    - Behavioural intervention only
    - Referral to hepatologist

    a. What specialist management would a hepatologist provide? How is this different to a behavioural intervention? Would this include any medication or interventions? Can you give approximate proportions of patients having each intervention?

Responses

#1	cirrhosis surveillance (HCC & Varices) if they have evidence of advanced liver fibrosis as well as provide behavioural intervention.

	In our practice, this is for people who do not have advance liver fibrosis and do not need surveillance but remain at risk of progressive liver fibrosis. If in secondary care, they can access trial medication – no licences treatment of liver fibrosis In our service i. 70% coming to community fibroscan service provided behavioural advice and discharged to GP with advice to repeat fibrosis assessment in 3-5 depending on risk factors. ii. 30% referred to hepatology from community fibroscan service (25% of these patients have Fibroscan result of >20kpa) a.iii. Patients with ELF<9.5 remained with GP to repeat fibrosis assessment in 3 years, these do to attend community fibroscan service.
#2	The hepatologist will assess for signs of portal hypertension and deranged liver function as well potentially exclude other causes of liver disease. Some of these patients may be eligible for clinical trials with new therapeutic agents. Other interventions depend on the cause of the liver disease.
#3	In patients with an indication for fibroscan there has in most cases been a reason for performing In my personal experience this results in the majority of patients receiving some intervention / lifestyle recommendations example form inner London acute setting 9 in 10 patients were sent back to primary care from secondary care who were referred for ABN LFT's as they had no fibrosis but high fat/steatosis on scanning – a risk for CVD, T2DM but can be managed highly effectively by primary care Figure below New Clinical pathway for NAFLD (AGA example)

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	**INDETERMINATE RISK** FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	**HIGH RISK**[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Footnotes:
1. Patients with F4 or cirrhosis (based on biopsy, LSM values based on vibration controlled transient elastography (VCTE, FibroScan®) or > 5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM > 20 kPa or platelet count of < 150,000/mm^3.
2. All patients require regular physical activity, healthy diet, avoid excess alcohol intake.
3. Weight loss recommended for cardiometabolic benefit and reversal of steatosis. Greater weight loss is often associated with more benefit, such as reversal of steatohepatitis (usually with weight loss ≥7%) or fibrosis (usually with weight loss ≥10%).
4. Individualize based on further work-up and efforts to confirm the diagnosis of NASH. A liver biopsy provides helpful information and should be considered for cases where there is a diagnostic doubt such as patients with indeterminate, unreliable, or conflicting non-invasive assessments or as part of phase 2 or 3 clinical trials.
5. No pharmacological agent is FDA-approved for the treatment of NASH. Patients with T2DM may benefit from some diabetes medications, such as pioglitazone [80, 81, 86, 87, 88] and some GLP-1 RAs [84, 85] that have reported histological improvement in RCTs in patients with NASH, either with or without diabetes. Among GLP-1 RAs, semaglutide has the strongest evidence of liver histological benefit [89].
6. Vitamin E improves steatohepatitis in patients with NASH without diabetes [80], with less evidence in patients with T2D [81].
7. Pharmacotherapy in patients with NASH cirrhosis is very limited and should be avoided until more data become available.
8. Statins can be used safely in patients with steatohepatitis and liver fibrosis; to be avoided in decompensated cirrhosis.

Figure 3. Management of NAFLD/NASH.

The monitoring of behavioural change with FibroScan is highly effective.

Medication and treatment options will be based on disease diagnosis, there are no current approved medications for NASH/NAFLD – lifestyle modification is the primary and most effective choice as it can be for Alcohol

#4	There are evidence based interventions for advanced liver disease/ cirrhosis (varices and HCC surveillance- see NICE guidelines). In addition hepatologists are asked to make a decision on which patients need further investigation in the intermediate range. I don't underatnd no behaviural intervention – If you have risk factors for liver disease you should have intervention, even if fibrosis marker is normal . For proportions of pateinst with severe liver disease and cirrhosis in the community you can be guided by the literature . We have published at least 3 studies in UK with this breakdown The Development and Implementation of a Commissioned Pathway for the Identification and Stratification of Liver Disease in the Community. Chalmers J, Wilkes E, Harris R, Kent L, Kinra S, Aithal GP, Holmes M, Johnson J, Morling JR, Guha IN. Frontline Gastroenterol. 2020 Feb 10;11(2):86-92. doi: 10.1136/flgastro-2019-101177. Epub 2019 Jun 26 Obesity Is the Most Common Risk Factor for Chronic Liver Disease: Results From a Risk Stratification Pathway Using Transient Elastography. Harris R, Card TR, Delahooke T, Aithal GP, Guha IN. Am J Gastroenterol. 2019 Nov;114(11):1744-1752. Obesity and type 2 diabetes are important risk factors underlying previously undiagnosed cirrhosis in general practice: a cross-sectional study using transient elastography. Harman DJ, Ryder SD, James MW, Wilkes EA, Card TR, Aithal GP, Guha IN. Aliment Pharmacol Ther. 2018 Feb;47(4):504-515. doi: 10.1111/apt.14463. Epub 2017 Dec 6.
#5	*What specialist management would a hepatologist provide*? NICE management of cirrhosis if present, endoscopy for varices, HCC surveillance *How is this different to a behavioural intervention? Would this include any medication or interventions*? There are medicines used in practice Vitamin E and pioglitazone, which have a small evidence base (PIVENS trial) and many will be offered therapy in trials now. *Can you give approximate proportions of patients having each intervention?* Around 10% cirrhosis. A further 20% offered some form of medical treatment. This will not be the case in non-trial centres, probably 10% treated with Pio/Vit E
#6	There are no approved drugs for NAFLD but the at-risk group can be referred for a multitude of drug trials by the treating Hepatologist. The Group with significant fibrosis and cirrhosis will need 6 monthly surveillance for liver tumours and to rule out complications.
#7	*What specialist management would a hepatologist provide?* Disease progression, offer more support with healthstyle choices, enrol the patient in hepatocellular carcinoma surveillance program, offer treatment for hepatitis B/C *How is this different to a behavioural intervention? Would this include any medication or interventions? Can you give approximate proportions of patients having each intervention?* Our fibroscan data shows 22% of patients have significant (11% in the cirrhotic range) fibrosis/cirrhosis on scanning. 63% have a score <7

b. In the comparator arm (those having FibroScan in hospital setting) those referred to hepatology have a follow-up outpatient visit with a consultant "in line with UK clinical practice". Does this accurately reflect practice, or would the FibroScan measurement be taken, results reviewed and specialist treatment all started within the same hospital appointment?

Responses

#1	In our setting we have the fibroscan in the clinic – we can preform the fibroscan, provide advice and discharge of they do not have evidence of advanced liver disease. These are slots that could be used for patient who need hepatology input and not use hepatology time to make a diagnosis of low levels of fibrosis.
#2	It depends on the cause of the liver disease.
#3	UK clinical practice is only available in a limited number of specialist settings – currently most settings do not have access to this technology or this clinical practice. Where access to Fibroscan is available this will depend on the models and availability of FibroScan service options available to the Trust. – mobile, outreach, in reach, fixed…. Real time Fibroscan is used in several specialist centres and patients can be referred back immediately to primary care on the first appointment, where this can occur in primary care these patients may avoid referral, increased costs and emotional impacts. in other settings the wait for the Fibroscan appointment can take several months and post pandemic may take a year and more which means significant delays to information, care and the condition of the liver altering positively or negatively in the meantime. Poor patient experience and increased anxiety. These patients would I suspect be assessed on only blood-based markers primarily where Fibroscan is not available – this is the current process for patients in most areas due to lack of current access to fibroscan
#4	I think this varies between centres and no uniform practice
#5	No I think they would have scan and then come for follow up in the majority. Some pathways do fibroscan before initial OPA (which is possible to do via triage at referral or for me with primary care requested fibroscan)
#6	There is quite a lot of variability of these specialist clinics. At the best end of spectrum the journey is one-stop with assessment and consultant review in one visit. In most settings the fibroscan test and consultant review may be two separate appointments.
#7	If the scan is done adhoc then treatment can be started at the same time as in hep C clinics. If in a dedicated fibroscan clinic a brief intervention maybe given (dependant on if the operator knows the patient history) but the report is sent back to the referrer. However the consultant follow up maybe a telephone clinic rather than face to face

5. What proportion of patients referred to secondary care attend and have FibroScan, but require no further management (i.e. inappropriate referral)?

Responses

#1	In our service, the discharge after first clinic consultant dropped from 35 to 25% after the introduction of the community fibroscan service.
#2	50 % in my experience
#3	An example based on 4000 patients reviewed - 92% of patients seen for abnormal LFT's were referred directly back to primary care for management of

	lifestyle as NO fibrosis was evident when FibroScanned – This meant at the time for many 3 specialist appointments - one initial then one for the fibroscan and the follow up. In other liver disease referrals this will alter, and the level of the specialist unit being referred to.
#4	See proportion answer further up
#5	Variable and depends on your referral pathway. Because we have FIB4/fibroscan triage there are few people seen with low fibroscans. In a more traditional pathway with no fibrosis marker it will be the majority, 75% at least.
#6	I don't think it is fair to call it inappropriate referral if the screening process i.e. NAFLD/Fib-4 has been used appropriately. The low risk cohort detected by Fibroscan actually don't need to be seen by a consultant if the tests are done in nurse-led clinics.
#7	There is no inappropriate referral rate. The GP's request them based on lifestyle (alcohol or obesity) or health issues and imaging such as fatty liver on USS in a diabetic. A negative scan is reassuring that nothing urgent needs to be done or that the liver is coping despite bad behaviours with room to improve.

6. The economic model assumes that patients scanned (in primary care or hospital setting), who require a behavioural intervention, have an additional separate GP appointment to deliver this.
    a. In primary care, would behavioural advice be delivered at the same GP appointment as the FibroScan measurement?

Responses

#1	Unlikely, fibroscan service would be separate to the GP consultation. In our service the behavioural advice is provided at the Fibroscan service by a nurse/trained health professional
#2	Could be delivered at the same appointment
#3	Depending on the model being used – if a specialist nurse or GP used to scan then advice may be given at the scan If a technician, then yes this would require additional time and appointment
#4	That approach makes the most sense
#5	There is no reason why fibroscanner cannot deliver the behavioural advice as part of the test. It requires a script (for alcohol we have developed this in the KLIFAD study). It wil depend on the clinicians views too, some will want to do this themselves although I am sure most would rather the fibroscanner did it!
#6	Not always
#7	This is possible but would need a dedicated session to take a history and address lifestyle factors as well as discuss the findings of the fibroscan

    b. In secondary care, would behavioural advice be delivered at the same hospital appointment as the FibroScan measurement?

Responses

#1	In our service, yes, fibroscan is performed at the first clinic consultation.
#2	Ideally, yes.
#3	As above – not all secondary care areas use nurses for all Fibroscan clinics and can used mixed models
#4	In our centre – yes
#5	Again it will vary, ideally the fibroscanner should deliver the advice and this may be repeated in clinic. Those with a high fibroscan will get a medical review so may get 2x lifestyle advice.
#6	Not always

#7	Yes, see the above answer

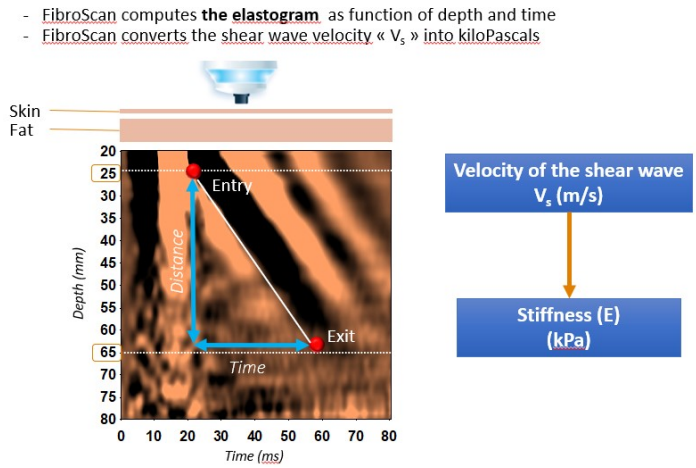
7. For experts with experience in using FibroScan in secondary care, can you advise which clinical codes (OPCS and HRG codes) are used to represent liver transient elastography within your centre?

Responses

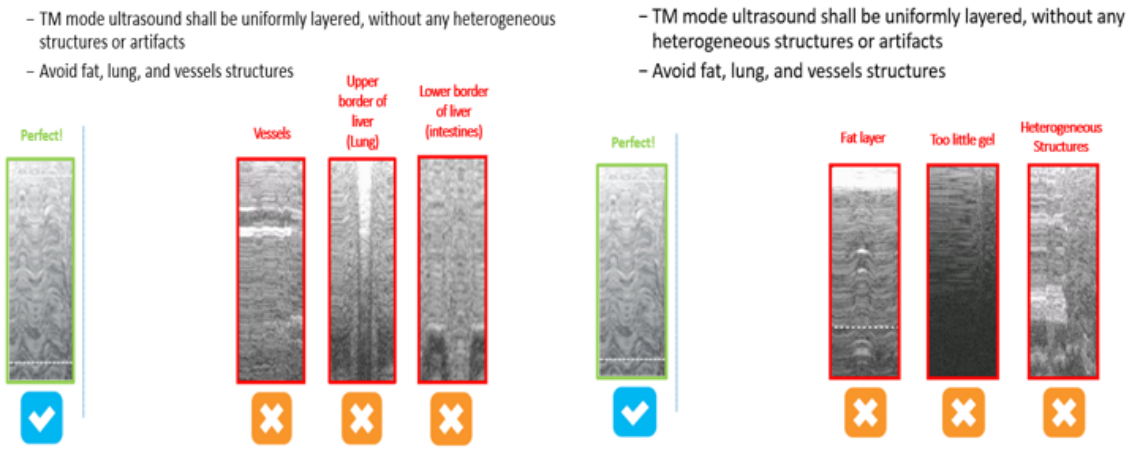
#1	In our service OPCS
#2	I am unaware of this I'm afraid
#3	There is no current standardisation for fibroscan cost and only 1 HRG4 tariff code - based on Radiology Tarif, Fibroscan is not delivered in radiology and the cost does not reflect equipment, training or access costs Several units cost through alternative Tariffs for specialist appointments, consultant codes as a result there is wide variation of cost
#4	I don't know
#5	Sorry no idea
#6	Not relevant in Scotland
#7	APT1765

8. At previous meeting it was discussed that users of FibroScan need to review the elastogram and not simply rely on the numerical output of the FibroScan device. Elastogram review is not explicitly reported in any of the published evidence, and the EAC assumes that this review would require some degree of training/experience. Is reliance on FibroScan numerical output without interpretation of the elastogram a major clinical concern?

Responses

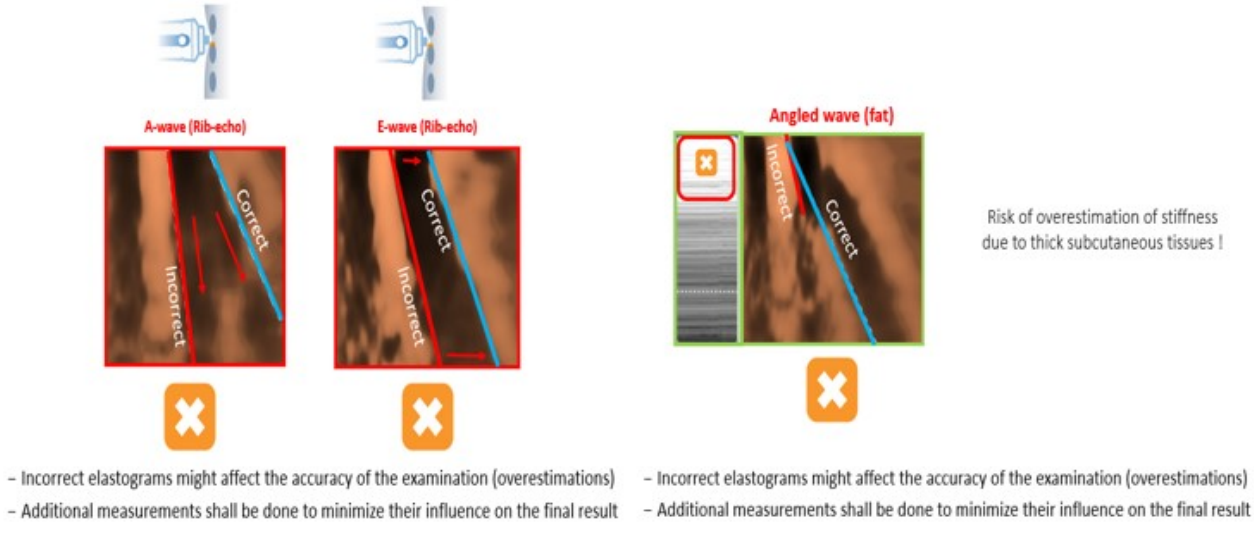
#1	In my opinion not a major clinic concern. The numerical value is good enough to differentiate between those with no liver fibrosis and those with advance fibrosis. It is not good enough for patients with moderate fibrosis but I don't think the elastogram help any further in this range.
#2	I think review of the elastrogram becomes more relevant if the readings are unsuccessful and there is a high IQR
#3	It is widely assumed that all Fibroscans are equal being based on a minimum of 10 readings and the intra and inter reproducibility being good that the readings in KPa and dB/m are enough.  Elastograms are images such as ECG readings are traces of heart electrical activity if this is performed poorly or not reviewed accurately it can lead to decisions based on incorrect information. This is less likely given the way FibroScan has been developed but there is a training and accreditation process that should not be weakened by allowing just anyone to scan. Knowing NORMAL, abnormal and incorrect elastograms for scans is essential

Assess to FibroScan should NOT result in the reduction of its quality and validity and should be

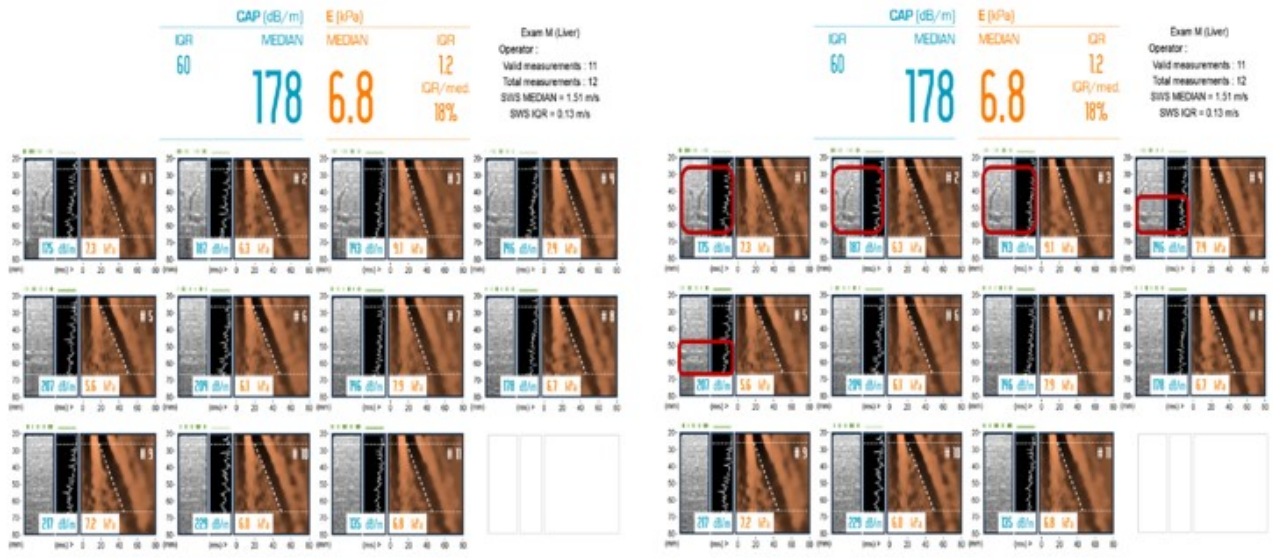


performed by skilled individuals!
Fully trained and correctly supervised operatives know the traces as they take them and should ensure these to be as accurate as possible. They should be able to note when it is incorrect – this results in confidence in the results for physicians.

A good knowledge of elastograms (A wave, E wave rib echos) and the quality of training and supervision is what ensures the quality and accuracy of the scan. This is specifically relevant to difficult to scan populations – large habitus



In a similar way ECG readings can also be misinterpreted if the process was done inaccurately. Ensuring training, supervision for proficiency (50 – 100 supervised scans currently recommended) is essential to maintain the results as accurate and equivocal in any setting.
The elastograms and quality of these are used in the supervision of those being trained and in many trusts training policies have been developed. It is not uncommon now to have someone trained who then shows someone else and this continues which poses risk and may significantly compromise quality and patient results.

	 A valid scan by all definitions - number, IQR/med but invalid due to the poor quality of the elastograms 50% have veins present which compromises the reading – possible underestimation of liver stiffness This is NOT the process all trained Fibroscan users are required to receive initial training by ECHOSENS. They then will undergo training and supervision by those skilled in Fibroscan in keeping with local governance policies. Anyone NOT trained by ECHOSENS is not a qualified user. This additionally invalidates any warrantee provided by ECHOSENS for the equipment which can prove highly costly in the event of breakage. Only a fully trained user should be performing this scan on patients/individuals, which should be specifically clarified in the publication of this guidance.
#4	Personally I am not sure this is a big concern
#5	No, afraid this is rubbish. The operators need to review the elastograms to ensure there readings are reliable, this is an integral part of doing a fibroscan and is not ever done by the person receiving the result-we would just look at the KpA numbers and the IQR to ensure reliable. The elastogram review is essentially part of the training of the fibroscan operator
#6	Review of Elastogram is not common practice and numerical scores and IQR are traditionally used to interpret data and reliability.
#7	Review of the elastogram is useful to ensure the probe is in the correct plane, this is useful for very high readings to confirm that the liver is being imaged. Experience will identify the right image

Appendix 8

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Company Engagement Meeting

FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care

Date: Wednesday 27 October 2021; Time: 10:00 am

Attendees:

Echosens: [redacted]

Newcastle External Assessment Centre (EAC): Kim Keltie, Rachel O'Leary, Andrew Sims, Kathryn Fletcher

NICE: Thomas Walker, Jacob Grant, Donna Barnes

Observing: Mark Kroese, Patrick McGinley

Documents

MIB: https://www.nice.org.uk/advice/mib216

MTG Scope: https://www.nice.org.uk/guidance/gid-mt562/documents/final-scope

1. Welcome and introductions

2. EAC clinical evidence review

23. The company identified 7 papers from their literature search. The EAC considered 3 of these as out of scope and identified an additional 15 papers from an independent search. In total, 19 publications based on UK-based studies were included in the clinical evidence review which included 10 non peer-reviewed abstracts. There is some overlap in the clinical evidence with multiple papers reporting different outcome measures or different time points from the same trial.

24. The papers were heterogeneous in nature and differed in population screened (diabetes, obesity, alcohol, hepatitis risk factors) and setting (GP, drug/alcohol clinic, homeless hostel, community/pop-up clinics). The results demonstrated versatility in the use of FibroScan outside a hospital setting, but also demonstrated wide

variability in liver assessment uptake (between 38 and 97% across included papers). Clinical experts advise that attendance rates at liver screening (using FibroScan) in primary/community setting exceed that in secondary care.

25. The EAC identified no published direct evidence that directly compared FibroScan in a primary/community setting with FibroScan conducted in a secondary/specialist setting (in line with the final scope). Variability in FibroScan measurements in the same patients taken with M+ and XL+ probes between +/- 5kPa was identified in a single paper that studied people with BMI>28 kg/m^2, which may be clinically important given recommended thresholds of 6-8 kPa to classify elevated transient elastography. However, within a primary/community care setting there is a lack of published evidence demonstrating test/re-test reliability using the same probe. Identified evidence reported rates of test failure and unreliable test results; however, these are likely to reduce with experience. None of the papers reported adverse events directly associated with the FibroScan.

26. Based on the clinical evidence reviewed, the EAC considers it plausible that earlier detection of liver fibrosis and cirrhosis in primary/community care can lead to earlier management. However the impact on referrals to secondary care are unclear due to variable thresholds and diagnostic pathways being described in the literature. There is no evidence to support that the use of FibroScan in primary care reduces time taken.

Summary of main issues: lack of comparative studies and test/retest.

3. Discussion about the issues raised in the clinical evidence review

Company acknowledge lack of direct comparator evidence. There are lots of different pathways within the UK and no official criteria to refer patients. Company is aware of studies collecting real-world evidence which are ongoing (the first of which will be a UK study). Company confirmed that the Southampton pilot was referenced in the clinical submission. EchoSens will provide more detail regarding ongoing real-world data studies.

Comparison of uptake across settings. KK confirmed no data to support this in clinical evidence submission. Scarred Liver Project started in 2013 – EchoSens will check with PI if there are any data available.

ACTION: EchoSens to provide additional information regarding ongoing studies collecting real-world evidence to NICE/EAC

4. Questions on the economic evidence submission (Appendix)

5. Next steps

ACTION: Company will submit responses by COP tomorrow (via NICE Docs). Additional information will be provided (CAP/CAPc) at same time.

EAC report submitted to NICE 16th Nov (NICE send to company on same day)

Company fact check comments due to be returned 19th Nov

Appendix: Questions from EAC (Echosens to provide written responses COP Thursday 28th)

1. In the model, the cost per scan per patient (for scan only) is cheaper in secondary care than primary care, which might make it difficult to justify moving scans into primary care. Can you please explain?

Answer: In the model, the cost per scan in secondary care is £43.93 (NHS reference cost for ultrasound elastography). It is assumed this is an average cost over the machine's lifespan, including maintenance costs, but that this does not capture the cost of interpreting the scan result (see response to Question 4). Fibroscan is not currently available in secondary care on a pay-per-scan basis, so there is an upfront cost for each machine (e.g. £70,000 for FibroScan 630 Expert with M Probe). The EAC have also suggested that the average cost applied be increased to £62.25 (see Question 3).

The cost per scan outside secondary care (i.e., in primary care) is £58. There was an error in the economic model input (see Question 2a and 2b). This reflects the cost of the equipment (machine and M and XL probes), maintenance costs and training costs. There is no upfront cost for the machine.

A comparison of the suggested cost in secondary care (£62.25) to the amended cost outside of secondary care (£58) shows the absolute cost per scan per patient (scan only) to be lower outside secondary and specialist care.

2. a) Page 25 of the Economic Submission states that "Customer pay £58 per patient exam completed" which we assume is the current Pay Per Exam pricing for the secondary care setting. However, the HRG/NHS reference cost (which includes FibroScan assessment) is less than this at £43.93 (which means that the cost of the scan is not covered). Can you please explain?

Answer: The Pay Per Exam price (£58) is a commercial agreement between Echosens and the FS Go/ 230 customer. There is no upfront cost for the machine and includes maintenance costs and training.

Page 25 in the Economic submission contains an error. The list price for Pay Per Exam (£58) should be used in the economic model for the cost of FibroScan outside of secondary care. Please also see response to Question 2b.

The Pay Per Exam price does not reflect the cost of FibroScan in the secondary care setting. This is reflected in the NHS Reference Cost for Ultrasound Elastography (see Question 3).

b) On page 25 of the Economic Submission, the cost per patient scan is given as £58. Can you please justify the cost per patient scan in primary care being £70?

Answer: The £70 was an error. It would also need updating at the bottom of page 25 of the report, and Table 7

For reference:

£70 was a fee charged by CCGs (average) to the patients for FibroScan to be performed in primary care, and this is not part of the business model going forward if the NHS were agree to reimburse FibroScan in primary care.

For 'all patients' this results in the revised Total cost per person in . Two scenarios have been provided: one in which only the cost of FibroScan outside secondary care is update, and one in which the cost of FibroScan outside secondary care and FibroScan inside secondary care is updated as recommended in Question 3.

Scan setting	Total cost per person	
	Cost of FibroScan outside secondary care= £58; Cost of FibroScan in secondary care= £43.93	Cost of FibroScan outside secondary care= £58; Cost of FibroScan in secondary care= £62.25
FibroScan outside of secondary or specialist care	£128.97	£128.97
FibroScan in secondary or specialist care	£180.70	£195.35
Incremental costs	*-£51.73*	*-£66.39*

3. The cost given for FibroScan (scan only) in secondary care is £43.93 and references HRG code RD48Z from NHS Reference costs 2019-20. However, the EAC has identified an average cost over 3688 scans of £62 for RD48Z HRG using 2019/20 NHS reference costs. Can you please check the source and provide detail of where £43.93 came from?

Answer: The cost of Outpatient Imaging Ultrasound Elastography (RD48Z) was applied in the economic model (£43.93). This is the recorded National Average Unit Cost in the NHS reference costs 2019-2020. This value was selected as it was labelled for outpatients (rather than Direct Access) and had the highest number of examinations (accounting for 76% of all ultrasound elastographies) and number of data submissions. This was considered a conservative choice.

If the EAC feel that an average across the three averages reported in the NHS reference costs is more reflective of the cost of Fibroscan in secondary care, then this value can be replaced in the economic model, as calculated in Table below.

Department Code	Department Name	Currency Code	Currency Description	Number of Examination (% of all examinations)	National Average Unit Cost	Weighted cost
IMAGDA	Imaging: Direct Access	RD48Z	Ultrasound Elastography	127 (3.44%)	£69.73	£2.40
IMAGOP	Imaging: Outpatient	RD48Z	Ultrasound Elastography	754 (20.44%)	£129.17	£26.41
IMAGOP	Imaging: Outpatient	RD48Z	Ultrasound Elastography	2807 (76.11%)	£43.93	£33.44
Sum						£62.25

4. The total cost given for FibroScan in secondary care has a combined "cost of scan" using HRG code RD48Z and an additional "staff time to perform and evaluate scan in secondary/specialist care" of £93.19. This staff time would already be included in the HRG cost for the scan. Can you please explain why additional staff time has been included?

Answer: The additional labour cost was added as there is a cost of someone to interpret the scan.

There is a difference in labour cost depending on whether the scan is performed in secondary care or outside secondary care which reflects the difference in requirements for interpretation of the scan results (non-Consultant led face-to-face appointment in hepatology department compared to nurse outside secondary and specialist care).

5. The "staff time to perform and evaluate scan outside of secondary or specialist care" is given as £42 per hour in the model and references PSSRU Unit Costs 2020. However, the EAC has identified that the practice nurse cost per hour is £38 from this source. Can you please check the source and provide detail of where £42 came from?

Answer: This value is from Table 10.2 in the PSSRU Unit Costs 2020 report. The cost including qualifications were used:

"Unit costs available 2019/2020 (costs including qualifications given in brackets):

£38 (£42) per hour"

6. The "General practitioner consultation" is £39.23 for 9.22 minutes and references PSSRU Unit Costs 2020. However, the EAC has identified that the GP consultation (excluding direct care) is £28 for 9.22 minutes, from this source. Can you please check the source and provide detail of where £39.23 came from?

Answer: Costs including direct care staff costs, qualification costs, and including carbon emissions were used. This is located in Table 10.3b in the PSSRU report. If the EAC believe the cost excluding direct care staff costs is more reflective, £34.20 can be used in the economic model.

10.3b General practitioner — unit costs

Unit cost 2019/2020	Including direct care staff costs		Excluding direct care staff costs	
	With qualification costs	Without qualification costs	With qualification costs	Without qualification costs
Annual (including travel)	£278,759	£236,114	£243,648	£201,003
Annual (excluding travel)	£277,659	£235,014	£242,548	£199,903
Per hour of GMS activity[1]	£156	£132	£136	£112
Per hour of patient contact[1]	£255	£217	£223	£184
Per minute of patient contact[1]	£4.30	£3.60	£3.70	£3.10
Per surgery consultation lasting 9.22 minutes[1]	£39	£33	£34	£28
Per patient contact lasting 9.22 minutes (including carbon emissions (6 KgCO2e)[2](carbon costs less than £1)	£39.23	£33.19	£34.20	£28.16
Prescription costs per			£22.10[3]	

7. The "referral to hepatologist from outside of secondary or specialist care" is £207.86 in the model and references 306 Hepatology WF01B from NHS Reference costs 2019-20. However, the EAC has identified that a consultant-led outpatient appointment with a hepatologist is £169 (using Total Outpatient Attendance tab). If you were to use the WF01B HRG code then the EAC identified an average cost from 2731 outpatient visits of £151. Can you please check the source and provide detail of where £207.86 came from?

Answer: 59,958 attendances were logged for a 'non-admitted face-to-face attendance, first' in the hepatology department under currency code WF01B, on the NHS Reference Costs 2019-20 'CL' (consultant led) sheet. This reports a national average unit cost of £207.86.

We recognise the value on the 'Total Outpatient Attendance' sheet under Consultant Led to be £169. However, this does not make the distinction between first and follow-up appointments, which is why the value defined above was preferred. This value could be used in a sensitivity analysis.

The value of £151 quoted above can be located on the 'Total HRG' sheet, but this is not department specific. The hepatology department specific cost located on the CL sheet as defined above is preferred for this reason.

8. The "follow-up visit to hepatologist after scan in secondary or specialist care" is £164.75 in the model and references 306 Hepatology WF01A from NHS Reference costs 2019-20. However, the EAC has identified that a consultant-led outpatient appointment with a hepatologist is £169 (using Total Outpatient Attendance tab). If you were to use the WF10A HRG code then the EAC identified an average cost from 8061 outpatient visits of £125. Can you please check the source and provide detail of where £164.75 came from?

Answer: 195,167 attendances were logged for a 'non-admitted face-to-face attendance, follow-up' in the hepatology department under currency code WF01A, on the NHS Reference Costs 2019-20 'CL' (consultant led) sheet. This reports a national average unit cost of £164.75.

We recognise the value on the 'Total Outpatient Attendance' sheet under 'Total' to be £169. However, this does not make the distinction between first and follow-up appointments, which is why the value defined above was preferred. This value could be used in a sensitivity analysis.

The value of £125 quoted above can be located on the 'Total HRG' sheet, but this is not department specific. The hepatology department specific cost located on the CL sheet as defined above is preferred for this reason.

9. On page 20 of the Economic Submission, you state that "for a small proportion of patients, the scan may fail to produce results", and that some cases of liver disease may therefore be missed and remain untreated. This is not listed in the assumptions table on page 21, and therefore not justified, so could you please justify this assumption?

Answer:

Assumption	Justification
For a small proportion of patients receiving a scan, the scan fails to produce results (5%). This was based on an average from clinical studies reported in the clinical evidence section	Mansour 2021: 9% had an invalid reading. Harman 2015: Valid liver stiffness acquisition was possible in 97% of patients (3% invalid) Harris 2019: 93% had a reliable reading (7% invalid) Harman 2018: 98% had valid measurements (2% invalid) The average of these 'invalid' proportions is 5%.
References: Mansour D, Grapes A, Herscovitz M, Cassidy P, Vernazza J, Broad A, et al. Embedding assessment of liver fibrosis into routine diabetic review in primary care. JHEP Rep. août 2021;3(4):100293. Harman DJ, Ryder SD, James MW, Jelpke M, Ottey DS, Wilkes EA, et al. Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography. BMJ Open. 3 mai 2015;5(4):e007516-e007516. Harris R, Card TR, Delahooke T, Aithal GP, Guha IN. Obesity Is the Most Common Risk Factor for Chronic Liver Disease: Results From a Risk Stratification Pathway Using Transient Elastography. Am J Gastroenterol. nov 2019;114(11):1744-52.	

Harman DJ, Ryder SD, James MW, Wilkes EA, Card TR, Aithal GP, et al. Obesity and type 2 diabetes are important risk factors underlying previously undiagnosed cirrhosis in general practice: a cross-sectional study using transient elastography. Aliment Pharmacol Ther. 2018;47(4):504-15.

10. You have provided an email regarding the Southampton CCG study to support some of the clinical parameters used in the model, but not marked this or the parameters within the Economic Submission as academic in confidence – can you please confirm if these parameters can be made publically available, in the interests of transparency, or if they need to be redacted.

Answer: We did not get Southampton feedback so far on a such short notice.

11. Also, do you know when the Southampton CCG study is likely to be published?

Answer: We do not have this information.

12 [Additional question]: what is the difference between CAP, CAPc, SmartDepth and SmartExam. These are referred to in the supporting documentation however no description of differences?

ACTION: company will provide summary of differences (using existing material).

Answer: please find in the response submission a slide deck presenting those differences.

13 [Additional question]: what is the difference between FibroScan 430 mini/mini+?

Answer: 430 mini provides kPa only, 430 mini+ provides kPa and CAP.

14 [Additional question]: Economic model starts with FIB4. Can you explain why?

Answer: FIB-4 is recommended in EASL guidelines. However practice is variable. Some centres use NAFLD, AST/ALT ratio, obesity only. No national guideline to instruct clinicians on specific pathway – it depends what they are looking for. FIB-4 is good because it's based on a readily available blood test and incurs no further cost.

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from Newcastle External Assessment Centre to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **19 November 2021** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Diagnostics Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

Sent 16 November 2021

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 10: Company is presented as EchoSens	The name should be Echosens	The name of the company does not have a capital S in the middle	Thank you for highlighting this, and apologies for mis-referencing your company name. The EAC has replaced throughout the document with the correct spelling.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 20: FibroScan is contraindicated for use on an organ other than the liver (eyes and mucosa must be avoided), on wounds, on patients with active implants such as pacemakers, defibrillators, pumps, and on pregnant women.	This statement is only available in the US and in Japan	The use of FibroScan® medical devices on pregnant women and on patients with active implantable medical devices has been lifted since April 2016 (Manufacturer statement signed by our Chief Medical Officer). The statement was shared with NICE on October, 12th.	The IFU for FibroScan 230 GO (file named "MT562 Fibroscan E380M003.6_UserGuide_FS230_en-US 20210924DB [No ACIC]" dated July 2021) states the following contraindications in section 4.5: "To ensure patient safety, the FibroScan 230 must not be used in the following situations: On an organ other than the liver. On the eyes and mucosa. On wounds. On patients with active implants such as pacemakers, defibrillators, pumps, etc. On pregnant women." The EAC has added additional text to the "special considerations" to make this clearer.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 71: The EAC did not assess FibroScan training material, and therefore is unable to confirm whether elastogram review is included.	The future operators are trained to conduct a quality check of the elastogram during the training session.	This information is available in the training material support that we can share if needed.	Thank you for this clarification. The EAC has added this clarification to the section regarding training.

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 17: The Company launched SmartExam in 2021, which uses a new computation method of continuous CAP measurement (CAPc; also described in supporting documentation provided by the Company as second generation CAP).	The Company launched SmartExam in 2021, which uses a new computation method of CAP (continuous CAP or CAPc).	Echosens do not want the sentence “second generation” to be misleading for users, as the results and their interpretation remain the same.	Thank you for your comment. Apologies the EAC referred to second generation CAP as this is how it was referred in supporting documentation provided to NICE. The EAC has adjusted the wording.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 17: The Company has confirmed the first generation CAP measurement is available on	The Company has confirmed the first generation CAP measurement is available on FibroScan 502, FibroScan 502 Touch,	CAP is not available on S+ probe CAPc is available on S+ Probe	Thank you for this clarification. This differs to the information provided to the EAC in response to the emailed query

FibroScan 502, FibroScan 502 Touch, FibroScan 530 Compact, FibroScan 430 Mini/Mini+, FibroScan 630 Expert and FibroScan 230 Go, and that second generation CAPc measurement is available on FibroScan 502 Touch, FibroScan 530 Compact, FibroScan 430 Mini+, FibroScan 630 Expert and FibroScan 230 Go. The Company has confirmed that CAP and CAPc can be measured with all S+, M+ and XL+ probes.	FibroScan 530 Compact, FibroScan 430 Mini/Mini+, FibroScan 630 Expert and FibroScan 230 Go, and that second generation CAPc measurement is available on FibroScan 502 Touch, FibroScan 530 Compact, FibroScan 430 Mini+, FibroScan 630 Expert and FibroScan 230 Go. The Company has confirmed that **CAP can be measured with M+ and XL+ probes and CAPc can be measured with all S+, M+ and XL+ probes.**		(sent 01/11/21) as documented in the EAC Correspondence Log, 2021. However, the EAC has updated the report using the latest information provided by the Company at fact check.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
FibroScan 230 Go	FibroScan 230 GO	All mentions to FibroScan 230 GO should be in capital letters for “GO”	Thank you for this comment. The EAC has replaced this throughout the document.