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A decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multi-parametric magnetic resonance

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ABSTRACT

Objectives: The mortality associated with liver disease continues to increase despite the improvements implemented in the UK healthcare as does the prevalence of non-alcoholic fatty liver disease (NAFLD) given the escalating prevalence of obesity. The currently available methods to assess and monitor the stage of liver disease present several limitations. Recently, multi-parametric magnetic resonance (Liver*MultiScan*) has been developed to address these limitations. The aim of this study is to develop a decision analytic model for patients with suspected NAFLD, to investigate the effect of adding Liver*MultiScan* to the diagnostic pathway.

Perspective: The model takes the perspective of the NHS as the service provider.

Methods: A simple decision-tree model was developed to compare the costs associated with three diagnostic pathways for NAFLD that use non-invasive techniques. Firstly using Fibroscan alone, secondly using Liver*MultiScan* as an adjunct to Fibroscan, and thirdly, Liver*MultiScan* alone. The model was built to capture these clinical pathways, and used to compare the expected diagnostic outcomes and costs associated with each.

Results: The use of Liver*MultiScan* as an adjunct to Fibroscan, while increasing screening costs, is predicted to reduce the number of liver biopsies required by about 66%. Used as the sole diagnostic scan, there remains an expected 16% reduction in the number of biopsies required. There is a small drop in the overall diagnostic accuracy, as in the current model liver biopsy is presumed to give a definitive diagnosis.

Conclusion: The inclusion of Liver*MultiScan,* either as an adjunct to or replacement of Fibroscan, in the diagnostic pathway of NAFLD may lead to cost savings for the NHS if the model presumptions hold. Further high quality clinical evidence and cost data are required to test the model's predictions.

Strengths and limitations of this study

- This is the first study to evaluate the costs associated with the inclusion of a new method to assess liver disease in the diagnostic pathway of patients with suspected non-alcoholic fatty liver disease.
- Potential cost savings to the NHS have been identified by the use of Liver*MultiScan* as an adjunct or replacement of Fibroscan if the model presumptions hold.
- The current decision analytic model compares only the diagnostic pathways; it does not consider the consequences of any diagnosis and does not follow the progression of liver disease in individuals.
- Additional high quality clinical evidence and cost data are necessary to further develop and test the models predictions.

INTRODUCTION

Liver disease refers to any disorder of the liver that leads to a reduction of its functioning. There are several types of liver disease including sequelae of hepatitis, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). Hepatitis B, hepatitis C, ALD and NAFLD have similar pathological spectra and disease may progress through simple hepatic steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma.[1, 2] Hepatitis B and hepatitis C virus can be spread by semen as well as blood. Although both viruses can be spread through birth, sexual contact, and sharing of infected needles, hepatitis B virus is more likely to be spread at birth or sexual contact, while hepatitis C infection occurs more frequently through sharing of contaminated needles used to inject drugs. The clinical differentiation between ALD and NAFLD is usually performed by taking a history of a patient's alcohol intake combined with laboratory and imaging examinations. Patients with non-alcoholic steatohepatitis (NASH) usually exhibit more advanced fatty degeneration of liver cells than those with alcoholic steatohepatitis and the inflammatory infiltrate in NASH is somewhat less pronounced than in alcoholic steatohepatitis.[2]

Improvements made in UK healthcare have resulted in a decrease of mortality rates for most health conditions, including heart disease, endocrine or metabolic disease, respiratory disease and diabetes.[3] Liver disease is the exception. The standardised mortality rate has increased by almost 500% since 1970 in patients younger than 65 years.[3] Liver disease accounts for 62,000 years of working life lost every year; only ischaemic heart disease (74,000 years) and self-harm (71,000 years) lead to a greater premature loss of life.[4]

Between 1988 and 2008, the prevalence of chronic liver disease caused by hepatitis B virus, hepatitis C virus, and alcoholic liver disease has remained stable.[5] During the same period, the prevalence of NAFLD increased from 5.51% to 11.01%.[5] It is expected that the prevalence of NAFLD will continue to increase given the escalating prevalence of obesity; with projections to the year 2030 estimating a 33% increase in obesity and a 130% increase in severe obesity.[6]

Fatty liver (i.e. simple steatosis) was believed to be a benign condition with no or minimal rate of progression. However, recent evidence suggests that a substantial proportion of patients with simple steatosis progress towards NASH and fibrosis.[7-9] In most patients NASH develops on a background of diabetes or impaired glucose tolerance in the long-term.[10] Progression to cirrhosis, hepatocellular carcinoma and increased mortality has been reported for patients with NASH.[11, 12]

It is important therefore, to detect liver disease at its early stages before progression into NASH, a cirrhotic stage or liver cancer. The early stages of NAFLD can be managed and may regress if lifestyle advice is provided and followed. Weight

reduction has been found to be associated with non-progressive disease.[9] The early detection of NAFLD is important to establish an effective course of treatment, and has the potential to reduce the economic burden of liver disease and save lives.[13]

Liver biopsy

Liver biopsy is currently considered as the reference standard for the diagnosis of liver disease. Liver biopsy is nevertheless imperfect when used to assess the extent of disease progression in terms of fibrotic transformation of liver tissue. This is because it allows examination of only a very small area of the liver, potentially missing the disease as changes within the liver can be patchy. In addition, there is variability in histological interpretation depending on the individual pathologist's experience.[14, 15] Liver biopsy is invasive and associated with a risk of haemorrhagic complications. It can also be painful and stressful for the patient as well as time consuming. It is a relatively costly procedure and has a low level of diagnostic performance for early stages of fibrosis.[16, 17] Liver biopsy may cause anxiety in patients, and has been found to be painful in up to 30% of cases.[18] A recent willingness to pay evaluation found that most patients (75%) who had undergone a liver biopsy (publicly funded in British Columbia) would be willing to self-pay for transient elastography (not publicly funded in British Columbia).[19] The majority of patients preferred the non-invasive transient elastography method, as it was associated with less discomfort during and after the scan, and no feelings of anxiety after the procedure was explained.[19] Only those patients with unknown liver disease were found to prefer liver biopsy. There is a need in the diagnostic and monitoring pathway for non-invasive methods to assess and monitor the stage of liver disease.

Transient elastography

Transient elastography (Fibroscan) is a non-invasive method to assess hepatic fibrosis using ultrasound readings to measure the velocity of an elastic shear wave transmitted through the liver.[20] It is a painless test for which sedation is not required, it is significantly less expensive than liver biopsy, and it has not been associated with any adverse treatment-effects.[15] However, despite being widely used, the cut-off values of liver stiffness for the different stages of liver fibrosis are not well established.[21] Using Fibroscan, significant variations in liver stiffness measurements related to operator and patient factors rather than to disease progression have been observed.[22] The variations in cut-off values and measurements using Fibroscan limit the effectiveness of transient elastography for monitoring and assessing the progression of liver fibrosis.[22] In addition, Fibroscan has a high failure rate, particularly among obese patients. The reported failure rates vary widely, ranging from 4.5% in a cohort of patients with chronic liver disease,[23] to 41% in a cohort of patients with BMI of 35 kg/m^2 or higher.[9] A five-year

prospective study of 13,369 examinations of patients with suspected chronic liver disease reported an average failure rate for Fibroscan of 18.4%.[24] The main factors influencing reliability were limited operator experience and obesity, particularly increased waist circumference. Sub-group analysis in this study found the failure rate ranging from 12% (BMI < 25) to 53% (BMI > 40).[24] Failure rates for Fibroscan are higher for obese patients as the ultrasound wave used by the probe can be strongly attenuated by fatty tissue.[25] This limitation is important as obese patients have an increased risk of liver disease progression.

Multi-parametric magnetic resonance

Multi-parametric magnetic resonance is a new non-invasive technique designed to diagnose liver fibrosis. It consists of software (Liver*MultiScan*) that enables the assessment of multi-parametric liver data (i.e. fat, iron, and fibrosis) based on a magnetic resonance (MR) scan. The first study on this technology reported an average scan time of 23 minutes.[26] Transverse abdominal T1 and T2* MR maps, corresponding to segment 8 of the liver are acquired.[26] The majority of percutaneous liver biopsies are taken from this area. Once the image is acquired, an operator defines a region of interest of the liver lobe, away from vascular and biliary structures. The image is analysed remotely, removing the need for interpretation by a radiologist, potentially reducing the time needed for scan results and costs. The software generates a report for the clinician, with analyses of fat, iron and fibrosis levels in the liver. Liver*MultiScan* has been included as the only liver imaging test in the UK Biobank study.

Aim of the study

The aim of this study was to develop a preliminary decision analytic model of the diagnostic pathways for patients with suspected NAFLD using two non-invasive methods: (i) transient elastography and (ii) multi-parametric magnetic resonance.

METHODS

Modelling methodology

A simple decision-tree model was constructed in Excel to compare the costs associated with three diagnostic pathways for NAFLD that use non-invasive techniques. Firstly, using Fibroscan alone, then using Liver*MultiScan* as an adjunct to Fibroscan, and finally using Liver*MultiScan* alone (Figure 1). The model was built to capture these clinical pathways, and used to compare the expected diagnostic outcomes and costs associated with each.

(Insert Figure 1 here)

The first patient pathway uses Fibroscan as the first-line non-invasive diagnosis. Patients whose test results are within the normal range are referred back to their general practitioner and no further immediate tests are carried out. Patients giving a positive test move on to the next stage in the diagnostic pathway, which in this case is a confirmatory liver biopsy. Patients for whom the test failed also move on to the next stage of liver biopsy.

In the second pathway, Liver*MultiScan* is introduced as a second line, non-invasive diagnostic tool for those patients for whom the Fibroscan either gave a positive diagnosis or failed, and who would otherwise have had a liver biopsy at this stage. For those with a positive Fibroscan, a further positive diagnosis with Liver*MultiScan* is considered as confirmatory with no further tests necessary, whereas a contradictory negative test or a failure results in a liver biopsy. For those patients for whom the initial Fibroscan failed, Liver*MultiScan* becomes the first line diagnosis whereby test outcomes are treated as with Fibroscan alone. That is, a normal result requires no immediate further action, a positive result would require a confirmatory biopsy, and a second failure would be followed by a diagnostic biopsy.

In the final pathway, Liver*MultiScan* replaces Fibroscan as the first line diagnostic tool with test outcomes treated in the same way.

Model parameters

A hypothetical cohort of 1000 patients with suspected NAFLD was modelled. The estimated prevalence for the successive stages of fibrosis in the cohort was taken from a recent Health Technology Assessment (HTA).[27] In their analysis, 48 studies were used to assess the sensitivity and specificity of a number of diagnostic tools at successive thresholds of liver fibrosis. Overall prevalence at each threshold was calculated from the populations in the included studies. The median prevalence (minimum–maximum) of fibrosis stages F1–F4 in the studies identified, as well as additional model parameters, are presented in Table 1. The median prevalence at each threshold was taken to calculate prevalence for each level of fibrosis in the modelled population.

In the model, the sensitivity and specificity of Fibroscan at each threshold, as calculated in the HTA, were used to predict the proportion of positive and negative test results. For Liver*MultiScan*, sensitivity and specificity for any level of fibrosis were taken from Banerjee et al.[26] For those in the modelled cohort with liver fibrosis, the relevant sensitivities of the tests were used to predict the rates for true positives and false negatives, while for those without fibrosis, the specificities were

used to predict the rates of false positives and true negatives. Rates for test failures for Liver*MultiScan* were provided by the manufacturer.

Costs

The model takes the perspective of the NHS as the service provider. The costs for Fibroscan and liver biopsy were derived from the HTA report [27] and inflated from 2012 to 2014 prices using the Personal Social Services Research Unit inflator.[28] A price for the Liver*MultiScan* procedure is not currently available. For the base case analysis we presumed the cost of Liver*MultiScan* to be the same as Fibroscan. Cost-effectiveness thresholds for Liver*MultiScan* were evaluated for each of the diagnostic pathways with this diagnosis option. Given the short modelling horizon of the diagnostic pathways, no costs were discounted.

Model parameter		Source
NAFLD prevalence		
Fibrosis stage	Median (minimum-maximum)	
F 1	0.588 (0.367-0.814)	Crossan et al. [27]
F 2	0.319 (0.119-0.526)	Crossan et al. [27]
F 3	0.186 (0.050-0.440)	Crossan et al. [27]
F 4	0.128 (0.039-0.907)	Crossan et al. [27]
Sensitivity of Fibroscan for diagnosis of NAFLD		
Fibrosis stage	Summary sensitivity (95% CI)	
F ≥ 1	0.87 (0.81 to 0.92)	Crossan et al. [27]
F ≥ 2	0.79 (0.72 to 0.85)	Crossan et al. [27]
F ≥ 3	0.82 (0.74 to 0.88)	Crossan et al. [27]
F ≥ 4	0.96 (0.83 to 0.99)	Crossan et al. [27]
Specificity of Fibroscan for diagnosis of NAFLD		
Fibrosis stage	Summary specificity (95% CI)	
F ≥ 1	0.76 (0.57 to 0.88)	Crossan et al. [27]
F ≥ 2	0.76 (0.71 to 0.80)	Crossan et al. [27]
F ≥ 3	0.84 (0.78 to 0.89)	Crossan et al. [27]
F ≥ 4	0.89 (0.85 to 0.92)	Crossan et al. [27]
Sensitivity of Liver*MultiScan* for diagnosis of NAFLD		
Any fibrosis	0.86	Banerjee et al. [26]
Specificity of Liver*MultiScan* for diagnosis of NAFLD		
Any fibrosis	0.93	Banerjee et al. [26]
Failure rates	Base case (range)	
Fibroscan	18.4% (12% to 50%)	Castéra et al. [24]
Liver*MultiScan*	5% (2.5% to 10%)	Manufacturer data
Costs		
Fibroscan	£52.44	Crossan et al. [27]
Liver biopsy	£983.70	Crossan et al. [27]

Table 1. Summary of model inputs

RESULTS

Diagnostic pathway

For the base case model, it is presumed that the diagnostic pathways as set out in Figure 1 are followed exactly. In practice these pathways, and the decision whether to take a liver biopsy at any stage, may vary between individual patients depending on other indications or clinical opinion. Using Fibroscan alone with the median values for sensitivity and specificity, the model suggests that for the cohort of 1000 patients with suspected NAFLD there would be 496 positive and 319 negative test results. With 184 failures, 680 patients would move to the next diagnostic level; which in this case is a liver biopsy. Based on the prevalence of fibrosis, and the specificity of Fibroscan, 64 patients with fibrosis would continue undiagnosed, giving a diagnostic accuracy for this pathway of 93.6% if liver biopsy is presumed to give a definitive diagnosis. Introducing Liver*MultiScan* as a second line diagnostic tool before liver biopsy requires a further 680 Liver*MultiScan* tests for those patients thus indicated, but is predicted to more than halve the total number of liver biopsies required to 254. With the reduced number of biopsies, the overall diagnostic accuracy falls to 91.6%, with 78 patients with fibrosis remaining undiagnosed and 5 patients without fibrosis receiving an incorrect positive diagnosis. Using Liver*MultiScan* instead of Fibroscan would be expected to yield 508 positive and 442 negative test results. With 50 failures, 558 liver biopsies would then be indicated. The diagnostic accuracy for this pathway is 92.2%, with 78 undiagnosed cases of fibrosis.

Cost analysis

For Liver*MultiScan* to be a cost-efficient addition in the diagnosis of NAFLD, any increase in costs associated with its use, either as an adjunct to or instead of Fibroscan, needs to be compensated for by a reduction in the number of biopsies needed. As a reference point, if Liver*MultiScan* were to cost the same as Fibroscan, *i.e.* £52.44, the results outlined above would give the cost outcomes as summarised in Table 2.

	Fibroscan		Fibroscan plus Liver*MultiScan*		Liver*MultiScan*	
	Number	Cost	Number	Cost	Number	Cost
Fibroscan tests	1000	£52,440	1000	£52,440	0	£0
Liver*MultiScan* tests	0	£0	680	£35,684	1000	£52,440
Liver biopsies	679	£669,374	254	£249,902	558	£548,702
Total cost	£721,819		£338,026		£601,142	

Table 2. Base case results

When using Liver*MultiScan* as an adjunct to Fibroscan, the cost of the expected extra 680 tests is more than offset by the savings made by the reduction in the

number of biopsies required. When used instead of Fibroscan, the cost of testing remains the same, and there is some reduction in the number of expected biopsies, due to a lower failure rate and better diagnostic accuracy (mainly a better selectivity resulting in a lower rate of false positives).

Threshold and sensitivity analysis

The expected cost savings to be made in the two scenarios that use Liver*MultiScan* suggest that there is an opportunity to increase the price. When used as a second line diagnosis after Fibroscan, the use of Liver*MultiScan* remains cost effective up to £616 per test. This figure reflects the potential cost savings that could be made by performing these two types of scans before considering a biopsy. When used as the sole non-invasive diagnostic tool prior to liver biopsy, Liver*MultiScan* remains a cost-effective replacement for Fibroscan up to a cost of £173 per test. This figure is lower than the previous threshold as in this scenario there is again just one scanning method used before a possible biopsy.

Probabilistic sensitivity analysis

The HTA report used the included studies to calculate the sensitivity and specificity of Fibroscan, reporting mean values with 95% confidence intervals.[27] Probabilistic sampling was done on these distributions to assess the robustness of the deterministic estimate of cost-effectiveness when using Fibroscan and Liver*MultiScan* in combination. The results of the random sampling show a standard deviation in the cost difference of £42 per test, suggesting that there is a 95% probability of this strategy remaining cost effective up to a price threshold of £547.

Threshold analysis

Setting the sensitivity and specificity of Fibroscan at the lower and upper 95% confidence intervals gives break-even prices for Liver*MultiScan* when used in conjunction with Fibroscan of £558 and £659 respectively. The price of Liver*MultiScan* therefore needs to be reduced if the performance of Fibroscan is set to the most pessimistic levels. This is because Fibroscan gives an increase in the proportion of positive results (from 41% to 53%) at this lower diagnostic accuracy. These patients then go on to Liver*MultiScan* and, as their Fibroscan results are less accurate, they are more likely to be contradicted by Liver*MultiScan*. It is these patients with contradictory results who then go on for a liver biopsy. The model predicts that the percentage of the original cohort in this category would rise from 9.5% at the upper confidence level to 18% at the lower confidence level. Thus a more accurate Fibroscan means fewer contradictory results, with fewer resultant biopsies. In the third treatment pathway of Liver*MultiScan* alone, the corresponding break-even costs are £203 for the lower confidence interval, and £156 for the upper confidence interval.

Fibroscan and Liver*MultiScan* failure rate

Both Fibroscan and Liver*MultiScan* can fail or give unreliable results. This is caused by patient characteristics, technical issues with the equipment, or operator inexperience. As NAFLD is associated with higher BMI, it might be expected that the failure rate for Fibroscan in NAFLD patients would be higher than the 18.4% average reported in the Castéra et al. study.[24] However, with a lack of evidence to quantify any difference in average BMI of the two patient groups, and the subsequent effect on Fibroscan failure rates, the figure of 18.4% was used in the model as a conservative estimate of the baseline failure rate. For Liver*MultiScan,* BMI is less of an issue, with failures related more to technical issues. Trials by the manufacturer have indicated a failure rate in the range of approximately 2.5% to 5% associated with the use of Liver*MultiScan*.

With these figures in mind, Tables 3a and 3b show an illustrative range of failure rates for Fibroscan and Liver*MultiScan,* with the estimated break-even cost of Liver*MultiScan* when used as an adjunct to or replacement for Fibroscan respectively.

Liver*MultiScan* failure rate	Fibroscan failure rate			
	12%	18%	35%	50%
2.5%	£654	£638	£581	£543
5%	£638	£617	£567	£529
10%	£604	£585	£537	£501

Table 3a. Break-even cost of Liver*MultiScan* when used as an adjunct to Fibroscan

Liver*MultiScan* failure rate	Fibroscan failure rate			
	12%	18%	35%	50%
2.5%	£159	£221	£248	£306
5%	£148	£210	£237	£294
10%	£145	£187	£214	£271

Table 3b. Break-even cost of Liver*MultiScan* when used as a replacement for Fibroscan

In the first scenario, as the failure rate of Fibroscan increases, a higher proportion of patients move on to the second line diagnosis, with an associated increase in the total number of biopsies. With the extra cost of these biopsies the break-even price of Liver*MultiScan* decreases. In the second scenario, as the failure rate of Fibroscan goes up, the break-even price of Liver*MultiScan* also goes up, as it is now replacing a decreasingly reliable Fibroscan. In both scenarios the breakeven price of Liver*MultiScan* decreases with increased failures, as any extra failures at this stage mean extra liver biopsies.

Liver*MultiScan* as the sole diagnostic test

For the third diagnostic pathway in Figure 1, Liver*MultiScan* replaces Fibroscan as the first-line diagnostic test. In the modelled base-case for this scenario, as with Fibroscan, patients receiving a positive diagnosis go on for a confirmatory biopsy to assess the nature and extent of any fibrosis. If it can be shown that Liver*MultiScan* is able to match the diagnostic accuracy of liver biopsy in this role, then there is the potential for it to replace biopsy as the definitive diagnosis of liver fibrosis. Incorporating this possibility into the model reduces the number of biopsies by 508 per 1000 patients, the expected number of positive Liver*MultiScan* tests; leaving biopsies for just the 5% of patients for whom the Liver*MultiScan* fails. Obviating the need for biopsies for those patients with positive Liver*MultiScan,* reduces the total testing costs to 14% of those in the first scenario of Fibroscan backed up with liver biopsy. This means that the price of Liver*MultiScan* could remain cost effective up to a price of £672, if used as the sole diagnostic test replacing the combination of Fibroscan and liver biopsy. Removing biopsy as the second line test inevitably has an effect on the overall diagnostic accuracy of this pathway, reducing the rate of correct diagnoses to 89%, with 78 cases of fibrosis remaining undiagnosed and 27 patients without fibrosis receiving a false positive test result.

DISCUSSION

This study proposes that the current NAFLD diagnostic pathway may become more cost-efficient with the inclusion of Liver*MultiScan* either as an adjunct to or replacement of Fibroscan. The use of Liver*MultiScan* as an adjunct to Fibroscan has the potential to reduce the number of liver biopsies by 66% while as a replacement would result in a decrease in the number of biopsies needed of 16%. Acquisition of further clinical evidence is required to confirm if the use of Liver*MultiScan* as an adjunct or replacement of Fibroscan can result in cost savings for the NHS. Given the increasing prevalence of obesity, it is possible that Liver*MultiScan* will become more useful considering Fibroscan's unreliability and failed measurements associated with increased BMI.[24] Moreover, it has been observed that the rate of un-interpretable results with Fibroscan (due to fewer than 10 valid measurements) is 9.6%, a value that could be an under-estimation due to potential under-reporting.[27] The relationship between BMI and the prevalence of each stage of fibrosis has not been quantified, limiting any assessment of how the increased failure rate associated with obesity affects the diagnostic accuracy.

Controversy remains regarding the optimal cut-off values to diagnose advanced fibrosis using Fibroscan as the cut-off values differ across aetiologies. This leads to variation in the interpretation of Fibroscan results.[25] Initial findings suggest that Liver*MultiScan* can quantify the severity of liver disease.[26] This has implications in

the monitoring and evaluation of liver disease progression. Currently, repeated liver biopsies are necessary to assess the stage liver disease. Both from a patient and payers perspective it would be preferable that progression of liver disease be evaluated by a non-invasive method capable of assessing the stage of the disease rather than by an invasive and more costly liver biopsy. Since increasing disease activity may also occur in patients with simple steatosis, all patients with NAFLD should undergo periodic disease progression assessment with lifestyle modification advice if appropriate.[9] The value of Fibroscan in detecting early stages of liver disease is limited. Results of patients with low-stage grades of fibrosis (F<2) have been associated with significantly reduced reproducibility when compared to those of patients with marked fibrosis.[9, 29]

The current decision analytic model aims to compare only the diagnostic pathways. It does not consider the consequences of any diagnosis, either correct or incorrect, or failures to diagnose, with subsequent short and long-term disease progression and associated treatment outcomes. Patients with suspected NAFLD whose tests are within the normal range with either Fibroscan or Liver*MultiScan* should subsequently be re-tested within a period of one to two years in order to capture any possible disease progression. The model does not follow the progression of liver disease in individuals. Rather, it presumes that the prevalence of the various levels of fibrosis in the population presenting with suspected fatty liver disease, and associated diagnostic outcomes, remain broadly the same whether patients be new or returning. A more comprehensive model could be developed to consider the longer-term progression of liver disease in individuals combined with the treatment outcomes associated with the diagnoses. This would need considerably more evidence, and the HTA was unable to identify robust cost and quality-adjusted life year estimates or data on treatment effectiveness to inform such a model.[27] Future research should attempt to address the shortcomings of currently available evidence for this patient population.

Based on current practice, the reference standard for this model was liver biopsy. However, this is an imperfect reference standard. A UK national audit found that samples were insufficient for diagnosis in 71 (2.04%) of 3472 cases.[30] Inadequate liver biopsies in which a focal lesion was present at imaging occurred in 82 (7.1%) of 1162 biopsies and in 37 (1.7%) of 2155 liver biopsies where a focal lesion was not present.[30] The all-cause mortality risk following liver biopsy is approximately 0.2% with a higher risk of major bleeding.[31] Although this risk is substantially lower than previous reports, it should be noted that both Fibroscan and Liver*MultiScan* have not been associated with any serious side-effects. These aspects should be taken into account when modelling the long-term diagnostic pathways.

CONCLUSION

This study demonstrates that the inclusion of Liver*MultiScan* in the diagnostic pathway of NAFLD may lead to savings to the NHS if the model presumptions hold. Liver*MultiScan* could be included either as an adjunct to or replacement of Fibroscan, with both scenarios presenting savings compared to the current pathway to initial fatty liver diagnosis. In our model, the use of Liver*MultiScan* as an adjunct to Fibroscan is predicted to more than halve the number of biopsies required. It is important to generate additional high quality clinical evidence and cost data to develop the model further and test its predictions. If these studies show that Liver*MultiScan* is able to match the diagnostic accuracy of liver biopsy to quantify disease progression, then there is the potential for it to replace biopsy for the diagnosis of liver fibrosis, with significant cost savings to the healthcare provider.

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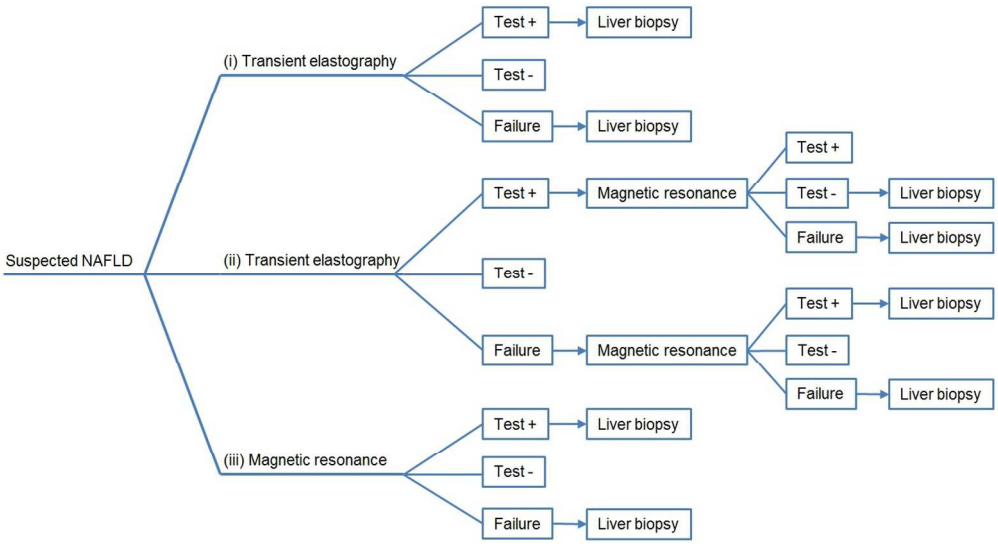

Decision analytic model of diagnostic pathways

391x211mm (96 x 96 DPI)

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

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

Section/item	Item No	Recommendation	Reported on page No/ line No
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.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
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.	3-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	4,5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	7
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.	N/A
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.	6, 7
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
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.	6, 7
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.	7
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.	5, 6
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	6, 7
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.	6, 7
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.	TABLE 1
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.	8 - 11
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	N/A

		of methodological assumptions (such as discount rate, study perspective).	
	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.	9, 10
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.	9, 10
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.	11-13
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.	13
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.	13

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

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A decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multi-parametric magnetic resonance

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A decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multi-parametric magnetic resonance

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Word count: 3951

ABSTRACT

Objectives: The mortality associated with liver disease continues to increase despite the improvements implemented in the UK healthcare as does the prevalence of non-alcoholic fatty liver disease (NAFLD) given the escalating prevalence of obesity. The currently available methods to assess and monitor the stage of liver disease present several limitations. Recently, multi-parametric magnetic resonance (Liver*MultiScan*) has been developed to address these limitations. The aim of this study is to develop a decision analytic model for patients with suspected NAFLD, to investigate the effect of adding Liver*MultiScan* to the diagnostic pathway.

Perspective: The model takes the perspective of the UK National Health Service (NHS) as the service provider.

Methods: A simple decision-tree model was developed to compare the costs associated with three diagnostic pathways for NAFLD that use non-invasive techniques. Firstly using Fibroscan alone, secondly using Liver*MultiScan* as an adjunct to Fibroscan, and thirdly, Liver*MultiScan* alone. The model was built to capture these clinical pathways, and used to compare the expected diagnostic outcomes and costs associated with each.

Results: The use of Liver*MultiScan* as an adjunct to Fibroscan, while increasing screening costs, is predicted to reduce the number of liver biopsies required by about 66%. Used as the sole diagnostic scan, there remains an expected 16% reduction in the number of biopsies required. There is a small drop in the overall diagnostic accuracy, as in the current model liver biopsy is presumed to give a definitive diagnosis.

Conclusion: The inclusion of Liver*MultiScan,* either as an adjunct to or replacement of Fibroscan, in the diagnostic pathway of NAFLD may lead to cost savings for the NHS if the model presumptions hold. Further high quality clinical evidence and cost data are required to test the model's predictions.

Strengths and limitations of this study

- This is the first study to evaluate the costs associated with the inclusion of a new method to assess liver disease in the diagnostic pathway of patients with suspected non-alcoholic fatty liver disease.
- Potential cost savings to the NHS have been identified by the use of Liver*MultiScan* as an adjunct or replacement of Fibroscan if the model presumptions hold.
- The current decision analytic model compares only the diagnostic pathways; it does not consider the consequences of any diagnosis and does not follow the progression of liver disease in individuals.
- Additional high quality clinical evidence and cost data are necessary to further develop and test the models predictions.

INTRODUCTION

Liver disease refers to any disorder of the liver that leads to a reduction of its functioning. There are several types of liver disease including sequelae of hepatitis, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). ALD and NAFLD have similar pathological spectra and disease may progress through simple hepatic steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma.[1, 2] The clinical differentiation between ALD and NAFLD is usually performed by taking a history of a patient's alcohol intake combined with laboratory and imaging examinations. Patients with non-alcoholic steatohepatitis (NASH) usually exhibit more advanced fatty degeneration of liver cells than those with alcoholic steatohepatitis and the inflammatory infiltrate in NASH is somewhat less pronounced than in alcoholic steatohepatitis.[2]

Improvements made in UK healthcare have resulted in a decrease of mortality rates for most health conditions, including heart disease, endocrine or metabolic disease, respiratory disease and diabetes.[3] Liver disease is the exception. The standardised mortality rate has increased by almost 500% since 1970 in patients younger than 65 years.[3] Liver disease accounts for 62,000 years of working life lost every year; only ischaemic heart disease (74,000 years) and self-harm (71,000 years) lead to a greater premature loss of life.[4]

Between 1988 and 2008, the prevalence of chronic liver disease caused by hepatitis B virus, hepatitis C virus, and alcoholic liver disease has remained stable.[5] During the same period, the prevalence of NAFLD increased from 5.51% to 11.01%.[5] It is expected that the prevalence of NAFLD will continue to increase given the escalating prevalence of obesity; with projections to the year 2030 estimating a 33% increase in obesity and a 130% increase in severe obesity.[6]

Fatty liver (i.e. simple steatosis) was believed to be a benign condition with no or minimal rate of progression. However, recent evidence suggests that a substantial proportion of patients (28-32%) with simple steatosis progress towards NASH and fibrosis within a three to four-year period.[7-9] In most patients NASH develops on a background of diabetes or impaired glucose tolerance in the long-term.[10] Progression to cirrhosis, hepatocellular carcinoma and increased mortality has been reported for patients with NASH.[11, 12]

It is important therefore, to detect liver disease at its early stages before progression into NASH, a cirrhotic stage or liver cancer. The early stages of NAFLD can be managed and may regress if lifestyle advice is provided and followed. Weight reduction has been found to be associated with non-progressive disease.[9] The early detection of NAFLD is important to establish an effective course of treatment, and has the potential to reduce the economic burden of liver disease and save lives.[13]

Liver biopsy

Liver biopsy is currently considered as the reference standard for the diagnosis of liver disease. Liver biopsy is nevertheless imperfect when used to assess the extent of disease progression in terms of fibrotic transformation of liver tissue. This is because it allows examination of only a very small area of the liver, potentially missing the disease as changes within the liver can be patchy. In addition, there is variability in histological interpretation depending on the individual pathologist's experience.[14, 15] Liver biopsy is invasive and associated with a risk of haemorrhagic complications. It can also be painful and stressful for the patient as well as time consuming. It is a relatively costly procedure and has a low level of diagnostic performance for early stages of fibrosis.[16, 17] Liver biopsy may cause anxiety in patients, and has been found to be painful in up to 30% of cases.[18] A recent willingness to pay evaluation found that most patients (75%) who had undergone a liver biopsy (publicly funded in British Columbia) would be willing to self-pay for transient elastography (not publicly funded in British Columbia).[19] The majority of patients preferred the non-invasive transient elastography method, as it was associated with less discomfort during and after the scan, and no feelings of anxiety after the procedure was explained.[19] Only those patients with unknown liver disease were found to prefer liver biopsy. There is a need in the diagnostic and monitoring pathway for non-invasive methods to assess and monitor the stage of liver disease.

Transient elastography

Transient elastography (Fibroscan) is a non-invasive method to assess hepatic fibrosis using ultrasound to measure the velocity of an elastic shear wave transmitted through the liver and assess liver stiffness.[20] It is a painless test for which sedation is not required, it is significantly less expensive than liver biopsy, and it has not been associated with any adverse treatment-effects.[15] However, despite being widely used, the cut-off values of liver stiffness for the different stages of liver fibrosis are not well established.[21] Using Fibroscan, significant variations in liver stiffness measurements related to operator and patient factors rather than to disease progression have been observed.[22] The variations in cut-off values and measurements using Fibroscan limit the effectiveness of transient elastography for monitoring and assessing the progression of liver fibrosis.[22] In addition, Fibroscan has a high failure rate, particularly among obese patients. The reported failure rates vary widely, ranging from 4.5% in a cohort of patients with chronic liver disease,[23] to 41% in a cohort of patients with BMI of 35 kg/m^2 or higher.[9] A five-year prospective study of 13,369 examinations of patients with suspected chronic liver disease reported an average failure rate for Fibroscan of 18.4%.[24] The main factors influencing reliability were limited operator experience and obesity, particularly increased waist circumference. Sub-group analysis in this study found

the failure rate ranging from 12% (BMI < 25) to 53% (BMI > 40).[24] Failure rates for Fibroscan are higher for obese patients as the ultrasound wave used by the probe can be strongly attenuated by fatty tissue.[25] This limitation is important as obese patients have an increased risk of liver disease progression.

Multi-parametric magnetic resonance

Multi-parametric magnetic resonance is a new non-invasive technique designed to diagnose liver fibrosis. It consists of software (Liver*MultiScan*) that enables the assessment of multi-parametric liver data (i.e. fat, iron, and fibrosis) based on a magnetic resonance (MR) scan. The first study on this technology reported an average scan time of 23 minutes and demonstrated that Liver*Multiscan* can quantify hepatic fibrosis, iron, and steatosis.[26] Transverse abdominal T1 and T2* MR maps, corresponding to segment 8 of the liver are acquired.[26] The majority of percutaneous liver biopsies are taken from this area. Once the image is acquired, an operator defines a region of interest of the liver lobe, away from vascular and biliary structures. The image is analysed remotely, removing the need for interpretation by a radiologist, potentially reducing the time needed for scan results and costs. The software generates a report for the clinician, with analyses of fat, iron and fibrosis levels in the liver. Liver*MultiScan* has been included as the only liver imaging test in the UK Biobank study.

Aim of the study

The aim of this study was to develop a preliminary decision analytic model of the diagnostic pathways for patients with suspected NAFLD using two non-invasive methods: (i) transient elastography and (ii) multi-parametric magnetic resonance.

METHODS

Modelling methodology

A simple decision-tree model was constructed in Excel to compare the costs associated with three diagnostic pathways for NAFLD that use non-invasive techniques. Firstly, using Fibroscan alone, then using Liver*MultiScan* as an adjunct to Fibroscan, and finally using Liver*MultiScan* alone (Figure 1). The model was built to capture these clinical pathways, and used to compare the expected diagnostic outcomes and costs associated with each.

(Insert Figure 1 here)

The first patient pathway uses Fibroscan as the first-line non-invasive diagnosis. Patients whose test results are within the normal range are referred back to their general practitioner and no further immediate tests are carried out. Patients giving a positive test move on to the next stage in the diagnostic pathway, which in this case is a confirmatory liver biopsy. Patients for whom the test failed also move on to the next stage of liver biopsy.

In the second pathway, Liver*MultiScan* is introduced as a second line, non-invasive diagnostic tool for those patients for whom the Fibroscan either gave a positive diagnosis or failed, and who would otherwise have had a liver biopsy at this stage. For those with a positive Fibroscan, a further positive diagnosis with Liver*MultiScan* is considered as confirmatory with no further tests necessary, whereas a contradictory negative test or a failure results in a liver biopsy. For those patients for whom the initial Fibroscan failed, Liver*MultiScan* becomes the first line diagnosis whereby test outcomes are treated as with Fibroscan alone. That is, a normal result requires no immediate further action, a positive result would require a confirmatory biopsy, and a second failure would be followed by a diagnostic biopsy.

In the final pathway, Liver*MultiScan* replaces Fibroscan as the first line diagnostic tool with test outcomes treated in the same way.

Model parameters

A hypothetical cohort of 1000 patients with suspected NAFLD was modelled. Initial clinical suspicion would be based on laboratory findings and the absence of other causes of liver disease. The estimated prevalence for the successive stages of fibrosis in the cohort was taken from a recent Health Technology Assessment (HTA).[27] In their analysis, 48 studies were used to assess the sensitivity and specificity of a number of diagnostic tools at successive thresholds of liver fibrosis. Overall prevalence at each threshold was calculated from the populations in the included studies. The median prevalence (minimum–maximum) of fibrosis stages F1–F4 in the studies identified, as well as additional model parameters, are presented in Table 1. The median prevalence at each threshold was taken to calculate prevalence for each level of fibrosis in the modelled population.

In the model, the sensitivity and specificity of Fibroscan at each threshold, as calculated in the HTA, were used to predict the proportion of positive and negative test results. For Liver*MultiScan*, sensitivity and specificity for any level of fibrosis were taken from Banerjee et al.[26] For those in the modelled cohort with liver fibrosis, the relevant sensitivities of the tests were used to predict the rates for true positives and false negatives, while for those without fibrosis, the specificities were used to predict the rates of false positives and true negatives. Rates for test failures for Liver*MultiScan* were provided by the manufacturer.

Costs

The model takes the perspective of the UK National Health Service (NHS) as the service provider. The costs for Fibroscan and liver biopsy were derived from the HTA report [27] and inflated from 2012 to 2014 prices using the Personal Social Services Research Unit inflator.[28] A price for the Liver*MultiScan* procedure is not currently available. For the base case analysis we presumed the cost of Liver*MultiScan* to be the same as Fibroscan. Cost-effectiveness thresholds for Liver*MultiScan* were evaluated for each of the diagnostic pathways with this diagnosis option. Probabilistic sensitivity analysis was conducted using the sensitivity and specificity of Fibroscan. Given the short modelling horizon of the diagnostic pathways, no costs were discounted.

Model parameter		Source
NAFLD prevalence		
Fibrosis stage	Median (minimum-maximum)	
F 1	0.588 (0.367-0.814)	Crossan et al. [27]
F 2	0.319 (0.119-0.526)	Crossan et al. [27]
F 3	0.186 (0.050-0.440)	Crossan et al. [27]
F 4	0.128 (0.039-0.907)	Crossan et al. [27]
Sensitivity of Fibroscan for diagnosis of NAFLD		
Fibrosis stage	Summary sensitivity (95% CI)	
F ≥ 1	0.87 (0.81 to 0.92)	Crossan et al. [27]
F ≥ 2	0.79 (0.72 to 0.85)	Crossan et al. [27]
F ≥ 3	0.82 (0.74 to 0.88)	Crossan et al. [27]
F ≥ 4	0.96 (0.83 to 0.99)	Crossan et al. [27]
Specificity of Fibroscan for diagnosis of NAFLD		
Fibrosis stage	Summary specificity (95% CI)	
F ≥ 1	0.76 (0.57 to 0.88)	Crossan et al. [27]
F ≥ 2	0.76 (0.71 to 0.80)	Crossan et al. [27]
F ≥ 3	0.84 (0.78 to 0.89)	Crossan et al. [27]
F ≥ 4	0.89 (0.85 to 0.92)	Crossan et al. [27]
Sensitivity of Liver*MultiScan* for diagnosis of NAFLD		
Any fibrosis	0.86	Banerjee et al. [26]
Specificity of Liver*MultiScan* for diagnosis of NAFLD		
Any fibrosis	0.93	Banerjee et al. [26]
Failure rates	Base case (range)	
Fibroscan	18.4% (12% to 50%)	Castéra et al. [24]
Liver*MultiScan*	5% (2.5% to 10%)	Manufacturer data
Costs		
Fibroscan	£52.44	Crossan et al. [27]
Liver biopsy	£983.70	Crossan et al. [27]

Table 1. Summary of model inputs

RESULTS

Diagnostic pathway

For the base case model, it is presumed that the diagnostic pathways as set out in Figure 1 are followed exactly. In practice these pathways, and the decision whether to take a liver biopsy at any stage, may vary between individual patients depending on other indications or clinical opinion. Using Fibroscan alone with the median values for sensitivity and specificity, the model suggests that for the cohort of 1000 patients with suspected NAFLD there would be 496 positive and 319 negative test results. With 184 failures, 680 patients would move to the next diagnostic level; which in this case is a liver biopsy. Based on the prevalence of fibrosis, and the specificity of Fibroscan, 64 patients with fibrosis would continue undiagnosed, giving a diagnostic accuracy for this pathway of 93.6% if liver biopsy is presumed to give a definitive diagnosis. Introducing Liver*MultiScan* as a second line diagnostic tool before liver biopsy requires a further 680 Liver*MultiScan* tests for those patients thus indicated, but is predicted to more than halve the total number of liver biopsies required to 254. With the reduced number of biopsies, the overall diagnostic accuracy falls to 91.6%, with 78 patients with fibrosis remaining undiagnosed and 5 patients without fibrosis receiving an incorrect positive diagnosis. Using Liver*MultiScan* instead of Fibroscan would be expected to yield 508 positive and 442 negative test results. With 50 failures, 558 liver biopsies would then be indicated. The diagnostic accuracy for this pathway is 92.2%, with 78 undiagnosed cases of fibrosis.

Cost analysis

For Liver*MultiScan* to be a cost-efficient addition in the diagnosis of NAFLD, any increase in costs associated with its use, either as an adjunct to or instead of Fibroscan, needs to be compensated for by a reduction in the number of biopsies needed. As a reference point, if Liver*MultiScan* were to cost the same as Fibroscan, *i.e.* £52.44, the results outlined above would give the cost outcomes as summarised in Table 2.

	Fibroscan		Fibroscan plus Liver*MultiScan*		Liver*MultiScan*	
	Number	Cost	Number	Cost	Number	Cost
Fibroscan tests	1000	£52,440	1000	£52,440	0	£0
Liver*MultiScan* tests	0	£0	680	£35,684	1000	£52,440
Liver biopsies	679	£669,374	254	£249,902	558	£548,702
Total cost	£721,819		£338,026		£601,142	

Table 2. Base case results

When using Liver*MultiScan* as an adjunct to Fibroscan, the cost of the expected extra 680 tests is more than offset by the savings made by the reduction in the

number of biopsies required. When used instead of Fibroscan, the cost of testing remains the same, and there is some reduction in the number of expected biopsies, due to a lower failure rate and better diagnostic accuracy (mainly a better selectivity resulting in a lower rate of false positives).

Threshold and sensitivity analysis

The expected cost savings to be made in the two scenarios that use Liver*MultiScan* suggest that there is an opportunity to increase the price. When used as a second line diagnosis after Fibroscan, the use of Liver*MultiScan* remains cost effective up to £616 per test. This figure reflects the potential cost savings that could be made by performing these two types of scans before considering a biopsy. When used as the sole non-invasive diagnostic tool prior to liver biopsy, Liver*MultiScan* remains a cost-effective replacement for Fibroscan up to a cost of £173 per test. This figure is lower than the previous threshold as in this scenario there is again just one scanning method used before a possible biopsy.

Probabilistic sensitivity analysis

The HTA report used the included studies to calculate the sensitivity and specificity of Fibroscan, reporting mean values with 95% confidence intervals.[27] Probabilistic sampling was done on these distributions to assess the robustness of the deterministic estimate of cost-effectiveness when using Fibroscan and Liver*MultiScan* in combination. The results of the random sampling show a standard deviation in the cost difference of £42 per test, suggesting that there is a 95% probability of this strategy remaining cost effective up to a price threshold of £547.

Threshold analysis

Setting the sensitivity and specificity of Fibroscan at the lower and upper 95% confidence intervals gives break-even prices for Liver*MultiScan* when used in conjunction with Fibroscan of £558 and £659 respectively. The price of Liver*MultiScan* therefore needs to be reduced if the performance of Fibroscan is set to the most pessimistic levels. This is because Fibroscan gives an increase in the proportion of positive results (from 41% to 53%) at this lower diagnostic accuracy. These patients then go on to Liver*MultiScan* and, as their Fibroscan results are less accurate, they are more likely to be contradicted by Liver*MultiScan*. It is these patients with contradictory results who then go on for a liver biopsy. The model predicts that the percentage of the original cohort in this category would rise from 9.5% at the upper confidence level to 18% at the lower confidence level. Thus a more accurate Fibroscan means fewer contradictory results, with fewer resultant biopsies. In the third treatment pathway of Liver*MultiScan* alone, the corresponding break-even costs are £203 for the lower confidence interval, and £156 for the upper confidence interval.

Fibroscan and Liver*MultiScan* failure rate

Both Fibroscan and Liver*MultiScan* can fail or give unreliable results. This is caused by patient characteristics, technical issues with the equipment, or operator inexperience. As NAFLD is associated with higher BMI, it might be expected that the failure rate for Fibroscan in NAFLD patients would be higher than the 18.4% average reported in the Castéra et al. study.[24] However, with a lack of evidence to quantify any difference in average BMI of the two patient groups, and the subsequent effect on Fibroscan failure rates, the figure of 18.4% was used in the model as a conservative estimate of the baseline failure rate. For Liver*MultiScan,* BMI is less of an issue, with failures related more to technical issues. Trials by the manufacturer have indicated a failure rate in the range of approximately 2.5% to 5% associated with the use of Liver*MultiScan*.

With these figures in mind, Tables 3a and 3b show an illustrative range of failure rates for Fibroscan and Liver*MultiScan,* with the estimated break-even cost of Liver*MultiScan* when used as an adjunct to or replacement for Fibroscan respectively.

Liver*MultiScan* failure rate	Fibroscan failure rate			
	12%	18%	35%	50%
2.5%	£654	£638	£581	£543
5%	£638	£617	£567	£529
10%	£604	£585	£537	£501

Table 3a. Break-even cost of Liver*MultiScan* when used as an adjunct to Fibroscan

Liver*MultiScan* failure rate	Fibroscan failure rate			
	12%	18%	35%	50%
2.5%	£159	£221	£248	£306
5%	£148	£210	£237	£294
10%	£145	£187	£214	£271

Table 3b. Break-even cost of Liver*MultiScan* when used as a replacement for Fibroscan

In the first scenario, as the failure rate of Fibroscan increases, a higher proportion of patients move on to the second line diagnosis, with an associated increase in the total number of biopsies. With the extra cost of these biopsies the break-even price of Liver*MultiScan* decreases. In the second scenario, as the failure rate of Fibroscan goes up, the break-even price of Liver*MultiScan* also goes up, as it is now replacing a decreasingly reliable Fibroscan. In both scenarios the break-even price of Liver*MultiScan* decreases with increased failures, as any extra failures at this stage mean extra liver biopsies.

Liver*MultiScan* as the sole diagnostic test

For the third diagnostic pathway in Figure 1, Liver*MultiScan* replaces Fibroscan as the first-line diagnostic test. In the modelled base-case for this scenario, as with Fibroscan, patients receiving a positive diagnosis go on for a confirmatory biopsy to assess the nature and extent of any fibrosis. If it can be shown that Liver*MultiScan* is able to match the diagnostic accuracy of liver biopsy in this role, then there is the potential for it to replace biopsy as the definitive diagnosis of liver fibrosis. Incorporating this possibility into the model reduces the number of biopsies by 508 per 1000 patients, the expected number of positive Liver*MultiScan* tests; leaving biopsies for just the 5% of patients for whom the Liver*MultiScan* fails. Obviating the need for biopsies for those patients with positive Liver*MultiScan,* reduces the total testing costs to 14% of those in the first scenario of Fibroscan backed up with liver biopsy. This means that the price of Liver*MultiScan* could remain cost effective up to a price of £672, if used as the sole diagnostic test replacing the combination of Fibroscan and liver biopsy. Removing biopsy as the second line test inevitably has an effect on the overall diagnostic accuracy of this pathway, reducing the rate of correct diagnoses to 89%, with 78 cases of fibrosis remaining undiagnosed and 27 patients without fibrosis receiving a false positive test result.

DISCUSSION

This study proposes that the current NAFLD diagnostic pathway may become more cost-efficient with the inclusion of Liver*MultiScan* either as an adjunct to or replacement of Fibroscan. The use of Liver*MultiScan* as an adjunct to Fibroscan has the potential to reduce the number of liver biopsies by 66% while as a replacement would result in a decrease in the number of biopsies needed of 16%. Acquisition of further clinical evidence is required to confirm if the use of Liver*MultiScan* as an adjunct or replacement of Fibroscan can result in cost savings for the NHS. Given the increasing prevalence of obesity, it is possible that Liver*MultiScan* will become more useful considering Fibroscan's unreliability and failed measurements associated with increased BMI.[24] Moreover, it has been observed that the rate of un-interpretable results with Fibroscan (due to fewer than 10 valid measurements) is 9.6%, a value that could be an under-estimation due to potential under-reporting.[27] The relationship between BMI and the prevalence of each stage of fibrosis has not been quantified, limiting any assessment of how the increased failure rate associated with obesity affects the diagnostic accuracy.

Controversy remains regarding the optimal cut-off values to diagnose advanced fibrosis using Fibroscan as the cut-off values differ across aetiologies. This leads to variation in the interpretation of Fibroscan results.[25] Initial findings suggest that Liver*MultiScan* can quantify the severity of liver disease.[26] This has implications in

the monitoring and evaluation of liver disease progression. Currently, repeated liver biopsies are necessary to assess the stage liver disease. Both from a patient and payers' perspective, it would be preferable that progression of liver disease be evaluated by a non-invasive method capable of assessing the stage of the disease rather than by an invasive and more costly liver biopsy. Since increasing disease activity may also occur in patients with simple steatosis, all patients with NAFLD should undergo periodic disease progression assessment with lifestyle modification advice if appropriate.[9] The value of Fibroscan in detecting early stages of liver disease is limited. Results of patients with low-stage grades of fibrosis (F<2) have been associated with significantly reduced reproducibility when compared to those of patients with marked fibrosis.[9, 29]

The current decision analytic model aims to compare only the diagnostic pathways. It does not consider the consequences of any diagnosis, either correct or incorrect, or failures to diagnose, with subsequent short and long-term disease progression and associated treatment outcomes. Patients with suspected NAFLD whose tests are within the normal range with either Fibroscan or Liver*MultiScan* should subsequently be re-tested within a period of one to two years in order to capture any possible disease progression. The model does not follow the progression of liver disease in individuals. Rather, it presumes that the prevalence of the various levels of fibrosis in the population presenting with suspected fatty liver disease, and associated diagnostic outcomes, remain broadly the same whether patients be new or returning. A more comprehensive model could be developed to consider the longer-term progression of liver disease in individuals combined with the treatment outcomes associated with the diagnoses. This would need considerably more evidence, and the HTA was unable to identify robust cost and quality-adjusted life year estimates or data on treatment effectiveness to inform such a model.[27] Future research should attempt to address the shortcomings of currently available evidence for this patient population.

Based on current practice, the reference standard for this model was liver biopsy. However, this is an imperfect reference standard. A UK national audit found that samples were insufficient for diagnosis in 71 (2.04%) of 3472 cases.[30] Inadequate liver biopsies in which a focal lesion was present at imaging occurred in 82 (7.1%) of 1162 biopsies and in 37 (1.7%) of 2155 liver biopsies where a focal lesion was not present.[30] The risk of excessive bleeding is about 1 in 500 to 1 in 1,000 and the risk of death is about 1 in 10,000 to 1 in 12,000.[31] Although this risk is substantially lower than previous reports, it should be noted that both Fibroscan and Liver*MultiScan* have not been associated with any serious side-effects. These aspects should be taken into account when modelling the long-term diagnostic pathways.

CONCLUSION

This study demonstrates that the inclusion of Liver*MultiScan* in the diagnostic pathway of NAFLD may lead to savings to the NHS if the model presumptions hold. Liver*MultiScan* could be included either as an adjunct to or replacement of Fibroscan, with both scenarios presenting savings compared to the current pathway to initial fatty liver diagnosis. In our model, the use of Liver*MultiScan* as an adjunct to Fibroscan is predicted to more than halve the number of biopsies required. It is important to generate additional high quality clinical evidence and cost data to develop the model further and test its predictions. If these studies show that Liver*MultiScan* is able to match the diagnostic accuracy of liver biopsy to quantify disease progression, then there is the potential for it to replace biopsy for the diagnosis of liver fibrosis, with significant cost savings to the healthcare provider.

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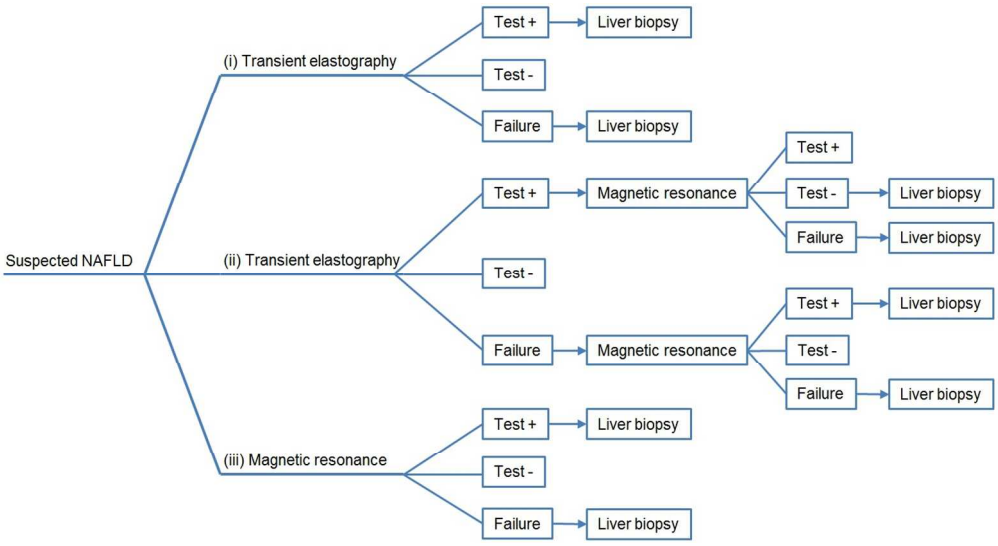

Decision analytic model of diagnostic pathways

391x211mm (96 x 96 DPI)

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

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

Section/item	Item No	Recommendation	Reported on page No/ line No
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.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
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.	3-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	4,5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	7
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.	N/A
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.	6, 7
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
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.	6, 7
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.	7
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.	5, 6
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	6, 7
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.	6, 7
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.	TABLE 1
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.	8 - 11
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	N/A

		of methodological assumptions (such as discount rate, study perspective).	
	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.	9, 10
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.	9, 10
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.	11-12
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.	13
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.	13

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

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A decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multi-parametric magnetic resonance imaging

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A decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multiparametric magnetic resonance imaging

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Keywords: decision analytic model, diagnostic pathways, multiparametric magnetic resonance imaging, non-invasive diagnosis, non-alcoholic fatty liver disease (NAFLD)

Word count: 4383

ABSTRACT

Objectives: The mortality associated with liver disease continues to increase despite the improvements implemented in the UK healthcare as does the prevalence of non-alcoholic fatty liver disease (NAFLD) given the escalating prevalence of obesity. The currently available methods to assess and monitor the stage of liver disease present several limitations. Recently, multiparametric magnetic resonance imaging (MRI) has been developed to address these limitations. The aim of this study is to develop a decision analytic model for patients with suspected NAFLD, to investigate the effect of adding multiparametric MRI to the diagnostic pathway.

Perspective: The model takes the perspective of the UK National Health Service (NHS) as the service provider.

Methods: A simple decision-tree model was developed to compare the costs associated with three diagnostic pathways for NAFLD that use non-invasive techniques. Firstly using transient elastography alone, secondly using multiparametric MRI as an adjunct to transient elastography, and thirdly, multiparametric MRI alone. The model was built to capture these clinical pathways, and used to compare the expected diagnostic outcomes and costs associated with each.

Results: The use of multiparametric MRI as an adjunct to transient elastography, while increasing screening costs, is predicted to reduce the number of liver biopsies required by about 66%. Used as the sole diagnostic scan, there remains an expected 16% reduction in the number of biopsies required. There is a small drop in the overall diagnostic accuracy, as in the current model liver biopsy is presumed to give a definitive diagnosis.

Conclusion: The inclusion of multiparametric MRI, either as an adjunct to or replacement of transient elastography, in the diagnostic pathway of NAFLD may lead to cost savings for the NHS if the model presumptions hold. Further high quality clinical evidence and cost data are required to test the model's predictions.

Strengths and limitations of this study

- This is the first study to evaluate the costs associated with the inclusion of a new method to assess liver disease in the diagnostic pathway of patients with suspected non-alcoholic fatty liver disease.
- Potential cost savings to the NHS have been identified by the use of multiparametric MRI as an adjunct or replacement of transient elastography if the model presumptions hold.
- The current decision analytic model compares only the diagnostic pathways; it does not consider the consequences of any diagnosis and does not follow the progression of liver disease in individuals.
- Additional high quality clinical evidence and cost data are necessary to further develop and test the model's predictions.

INTRODUCTION

Liver disease refers to any disorder of the liver that leads to a reduction of its functioning. There are several types of liver disease including sequelae of hepatitis, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). ALD and NAFLD have similar pathological spectra and disease may progress through simple hepatic steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma.[1, 2] The clinical differentiation between ALD and NAFLD is usually performed by taking a history of a patient's alcohol intake combined with laboratory and imaging examinations. Patients with non-alcoholic steatohepatitis (NASH) usually exhibit more advanced fatty degeneration of liver cells than those with alcoholic steatohepatitis and the inflammatory infiltrate in NASH is somewhat less pronounced than in alcoholic steatohepatitis.[2]

Improvements made in UK healthcare have resulted in a decrease of mortality rates for most health conditions, including heart disease, endocrine or metabolic disease, respiratory disease and diabetes.[3] Liver disease is the exception. The standardised mortality rate has increased by almost 500% since 1970 in patients younger than 65 years.[3] Liver disease accounts for 62,000 years of working life lost every year; only ischaemic heart disease (74,000 years) and self-harm (71,000 years) lead to a greater premature loss of life.[4]

Between 1988 and 2008, the prevalence of chronic liver disease caused by hepatitis B virus, hepatitis C virus, and alcoholic liver disease has remained stable.[5] During the same period, the prevalence of NAFLD increased from 5.51% to 11.01%.[5] It is expected that the prevalence of NAFLD will continue to increase given the escalating prevalence of obesity; with projections to the year 2030 estimating a 33% increase in obesity and a 130% increase in severe obesity.[6]

Fatty liver (i.e. simple steatosis) was believed to be a benign condition with no or minimal rate of progression. However, recent evidence suggests that a substantial proportion of patients (28-32%) with simple steatosis progress towards NASH and fibrosis within a three to four-year period.[7-9] In most patients NASH develops on a background of diabetes or impaired glucose tolerance in the long-term.[10] Progression to cirrhosis, hepatocellular carcinoma and increased mortality has been reported for patients with NASH.[11, 12]

It is important therefore, to detect fatty liver disease at its early stages before progression into NASH, a cirrhotic stage or liver cancer. The early stages of NAFLD can be managed and may regress if lifestyle advice is provided and followed. Weight reduction has been found to be associated with non-progressive disease.[9] The early detection of NAFLD is important to establish an effective course of treatment, and has the potential to reduce the economic burden of liver disease and save lives.[13] Recent EASL–EASD–EASO clinical practice guidelines have

recommended that all individuals with persistently abnormal liver enzymes or steatosis should be screened for NAFLD.[14]

Liver biopsy

Liver biopsy is currently considered as the reference standard for the diagnosis of liver disease. Liver biopsy is nevertheless imperfect when used to assess the extent of disease progression in terms of fibrotic transformation of liver tissue. This is because it allows examination of only a very small area of the liver, potentially missing the disease as changes within the liver can be patchy. In addition, there is variability in histological interpretation depending on the individual pathologist's experience.[15, 16] Liver biopsy is invasive and associated with a risk of haemorrhagic complications. It can also be painful and stressful for the patient as well as time consuming. It is a relatively costly procedure and has a low level of diagnostic performance for early stages of fibrosis.[17, 18] Liver biopsy may cause anxiety in patients, and has been found to be painful in up to 30% of cases.[19] A recent willingness to pay evaluation found that most patients (75%) who had undergone a liver biopsy (publicly funded in British Columbia) would be willing to self-pay for transient elastography (not publicly funded in British Columbia).[20] The majority of patients preferred the non-invasive transient elastography method, as it was associated with less discomfort during and after the scan, and no feelings of anxiety after the procedure was explained.[20] Only those patients with unknown liver disease were found to prefer liver biopsy. There is a need in the diagnostic and monitoring pathway for non-invasive methods to assess and monitor the stage of liver disease.

Transient elastography

Transient elastography is a non-invasive method to assess hepatic fibrosis using ultrasound to measure the velocity of an elastic shear wave transmitted through the liver and assess liver stiffness.[21] It is a painless test for which sedation is not required, it is significantly less expensive than liver biopsy, and it has not been associated with any adverse treatment-effects.[16] However, despite being widely used, the cut-off values of liver stiffness for the different stages of liver fibrosis are not well established.[22] Using transient elastography, significant variations in liver stiffness measurements related to operator and patient factors rather than to disease progression have been observed.[23] The variations in cut-off values and measurements limit the effectiveness of transient elastography for monitoring and assessing the progression of liver fibrosis.[23] In addition, transient elastography has a high failure rate, particularly among obese patients. The reported failure rates vary widely, ranging from 4.5% in a cohort of patients with chronic liver disease,[24] to 41% in a cohort of patients with BMI of 35 kg/m^2 or higher.[9] A five-year prospective study of 13,369 examinations of patients with suspected chronic liver disease reported an average failure rate for transient elastography of 18.4%.[25] The main

factors influencing reliability were limited operator experience and obesity, particularly increased waist circumference. Sub-group analysis in this study found the failure rate ranging from 12% (BMI < 25) to 53% (BMI > 40).[25] Failure rates for transient elastography are higher for obese patients as the ultrasound wave used by the probe can be strongly attenuated by fatty tissue.[26] This limitation is important as obese patients have an increased risk of liver disease progression.

Multiparametric magnetic resonance

Multiparametric magnetic resonance is a new non-invasive technique designed to diagnose liver fibrosis. It consists of software (Liver*MultiScan*) that enables the assessment of multiparametric liver data (i.e. fat, iron, and fibrosis) based on a magnetic resonance (MR) scan. The first study on this technology reported an average scan time of 23 minutes and demonstrated that multiparametric MRI can quantify hepatic fibrosis, iron, and steatosis.[27] Transverse abdominal T1 and T2* MR maps, corresponding to segment 8 of the liver are acquired.[27] The majority of percutaneous liver biopsies are taken from this area. Once the image is acquired, an operator defines a region of interest of the liver lobe, away from vascular and biliary structures. The image is analysed remotely, removing the need for interpretation by a radiologist, potentially reducing the time needed for scan results and costs. The software generates a report for the clinician, with analyses of fat, iron and fibrosis levels in the liver. Multiparametric MRI has been included as the only liver imaging test in the UK Biobank study.

Aim of the study

The aim of this study was to develop a preliminary decision analytic model of the diagnostic pathways for patients with suspected NAFLD using two non-invasive methods: (i) transient elastography and (ii) multiparametric magnetic resonance. Such a model could indicate the potential value of investment in further research and inform the design of such research.

METHODS

Modelling methodology

A simple decision-tree model was constructed in Excel to compare the costs associated with three diagnostic pathways for NAFLD that use non-invasive techniques. Firstly, using transient elastography alone, then using multiparametric MRI as an adjunct to transient elastography, and finally using multiparametric MRI alone (Figure 1). The chosen pathways were based on current clinical practice according to clinical advice. The model was built to capture these clinical pathways,

and used to compare the expected diagnostic outcomes and costs associated with each.

(Insert Figure 1 here)

For the base case model, it is presumed that the diagnostic pathways as set out in Figure 1 are followed exactly by all patients. In practice these pathways, and the decision whether to take a liver biopsy at any stage, may vary between individual patients depending on other indications or clinical opinion.

The first patient pathway uses transient elastography as the first-line non-invasive diagnosis. Patients whose test results are within the normal range are referred back to their general practitioner and no further immediate tests are carried out. Patients giving a positive test move on to the next stage in the diagnostic pathway, which in this case is a confirmatory liver biopsy. Patients for whom the test failed also move on to the next stage of liver biopsy.

In the second pathway, multiparametric MRI is introduced as a second line, non-invasive diagnostic tool for those patients for whom the transient elastography either gave a positive diagnosis or failed, and who would otherwise have had a liver biopsy at this stage. For those with a positive transient elastography, a further positive diagnosis with multiparametric MRI is considered as confirmatory with no further tests necessary, whereas a contradictory negative test or a failure results in a liver biopsy. For those patients for whom the initial transient elastography failed, multiparametric MRI becomes the first line diagnosis whereby test outcomes are treated as with transient elastography alone. That is, a normal result requires no immediate further action, a positive result would require a confirmatory biopsy, and a second failure would be followed by a diagnostic biopsy.

In the final pathway, multiparametric MRI replaces transient elastography as the first line diagnostic tool with test outcomes treated in the same way.

Model parameters

A hypothetical cohort of 1000 patients presenting with suspected NAFLD was modelled. Initial clinical suspicion would be based on laboratory findings and the absence of other causes of liver disease. The estimated prevalence for the successive stages of fibrosis in the cohort was taken from a recent Health Technology Assessment (HTA).[28] In their analysis, 48 studies were used to assess the sensitivity and specificity of a number of diagnostic tools at successive thresholds of liver fibrosis. Overall prevalence at each threshold was calculated from the populations in the included studies. The median prevalence (minimum–

maximum) of fibrosis stages F1–F4 in the studies identified, as well as additional model parameters, are presented in Table 1. The median prevalence at each threshold was taken to calculate prevalence for each level of fibrosis in the modelled population.

In the model, the sensitivity and specificity of transient elastography at each threshold, as calculated in the HTA, were used to predict the proportion of positive and negative test results. For multiparametric MRI, sensitivity and specificity for any level of fibrosis were taken from Banerjee et al.[27] For those in the modelled cohort with liver fibrosis, the relevant sensitivities of the tests were used to predict the rates for true positives and false negatives, while for those without fibrosis, the specificities were used to predict the rates of false positives and true negatives. Rates for test failures for multiparametric MRI were provided by the manufacturer.

Costs

The model takes the perspective of the UK National Health Service (NHS) as the service provider. The costs for transient elastography and liver biopsy were derived from the HTA report [28] and inflated from 2012 to 2014 prices using the Personal Social Services Research Unit inflator.[29] A price for the multiparametric MRI procedure is not currently available. For the base case analysis we presumed the cost of multiparametric MRI to be the same as transient elastography. Cost-effectiveness thresholds for multiparametric MRI were evaluated for each of the diagnostic pathways with this diagnosis option. Probabilistic sensitivity analysis was conducted using the sensitivity and specificity of transient elastography. Given the short modelling horizon of the diagnostic pathways, no costs were discounted.

Model parameter		Source
NAFLD prevalence		
Fibrosis stage	Median (minimum-maximum)	
F 1	0.588 (0.367-0.814)	Crossan et al. [28]
F 2	0.319 (0.119-0.526)	Crossan et al. [28]
F 3	0.186 (0.050-0.440)	Crossan et al. [28]
F 4	0.128 (0.039-0.907)	Crossan et al. [28]
Sensitivity of transient elastography for diagnosis of NAFLD		
Fibrosis stage	Summary sensitivity (95% CI)	
F ≥ 1	0.87 (0.81 to 0.92)	Crossan et al. [28]
F ≥ 2	0.79 (0.72 to 0.85)	Crossan et al. [28]
F ≥ 3	0.82 (0.74 to 0.88)	Crossan et al. [28]
F ≥ 4	0.96 (0.83 to 0.99)	Crossan et al. [28]
Specificity of transient elastography for diagnosis of NAFLD		
Fibrosis stage	Summary specificity (95% CI)	
F ≥ 1	0.76 (0.57 to 0.88)	Crossan et al. [28]
F ≥ 2	0.76 (0.71 to 0.80)	Crossan et al. [28]
F ≥ 3	0.84 (0.78 to 0.89)	Crossan et al. [28]
F ≥ 4	0.89 (0.85 to 0.92)	Crossan et al. [28]
Sensitivity of multiparametric MRI for diagnosis of NAFLD		
Any fibrosis	0.86	Banerjee et al. [27]
Specificity of multiparametric MRI for diagnosis of NAFLD		
Any fibrosis	0.93	Banerjee et al. [27]
Failure rates	Base case (range)	
Transient elastography	18.4% (12% to 50%)	Castéra et al. [25]
Multiparametric MRI	5% (2.5% to 10%)	Manufacturer data
Costs		
Transient elastography	£52.44	Crossan et al. [28]
Liver biopsy	£983.70	Crossan et al. [28]

Table 1. Summary of model inputs

RESULTS

Diagnostic pathway

Using transient elastography alone with the median values for sensitivity and specificity, the model suggests that for the cohort of 1000 patients with suspected NAFLD there would be 496 positive and 319 negative test results. With 184 failures, 680 patients would move to the next diagnostic level; which in this case is a liver biopsy. Based on the prevalence of fibrosis, and the specificity of transient elastography, 64 patients with fibrosis would continue undiagnosed, giving a diagnostic accuracy for this pathway of 93.6% if liver biopsy is presumed to give a definitive diagnosis. Introducing multiparametric MRI as a second line diagnostic tool before liver biopsy requires a further 680 multiparametric MRI tests for those patients thus indicated, but is predicted to more than halve the total number of liver biopsies required to 254. With the reduced number of biopsies, the overall diagnostic accuracy falls to 91.6%, with 78 patients with fibrosis remaining undiagnosed and 5 patients without fibrosis receiving an incorrect positive diagnosis. Using multiparametric MRI instead of transient elastography would be expected to yield 508 positive and 442 negative test results. With 50 failures, 558 liver biopsies would then be indicated. The diagnostic accuracy for this pathway is 92.2%, with 78 undiagnosed cases of fibrosis.

Cost analysis

For multiparametric MRI to be a cost-efficient addition in the diagnosis of NAFLD, any increase in costs associated with its use, either as an adjunct to or instead of transient elastography, needs to be compensated for by a reduction in the number of biopsies needed. As a reference point, if multiparametric MRI were to cost the same as transient elastography, *i.e.* £52.44, the results outlined above would give the cost outcomes as summarised in Table 2.

	Transient elastography		Transient elastography plus multiparametric MRI		Multiparametric MRI	
	Number	Cost	Number	Cost	Number	Cost
Transient elastography tests	1000	£52,440	1000	£52,440	0	£0
Multiparametric MRI tests	0	£0	680	£35,684	1000	£52,440
Liver biopsies	679	£669,374	254	£249,902	558	£548,702
Total cost	£721,819		£338,026		£601,142	

Table 2. Base case results

When using multiparametric MRI as an adjunct to transient elastography, the cost of the expected extra 680 tests is more than offset by the savings made by the

reduction in the number of biopsies required. When used instead of transient elastography, the cost of testing remains the same, and there is some reduction in the number of expected biopsies, due to a lower failure rate and better diagnostic accuracy (mainly a better selectivity resulting in a lower rate of false positives).

Threshold and sensitivity analysis

The expected cost savings to be made in the two scenarios that use multiparametric MRI suggest that there is an opportunity to increase the price. When used as a second line diagnosis after transient elastography, the use of multiparametric MRI remains cost effective up to £616 per test. This figure reflects the potential cost savings that could be made by performing these two types of scans before considering a biopsy. When used as the sole non-invasive diagnostic tool prior to liver biopsy, multiparametric MRI remains a cost-effective replacement for transient elastography up to a cost of £173 per test. This figure is lower than the previous threshold as in this scenario there is again just one scanning method used before a possible biopsy.

Probabilistic sensitivity analysis

The HTA report used the included studies to calculate the sensitivity and specificity of transient elastography, reporting mean values with 95% confidence intervals.[28] Probabilistic sampling was done on these distributions to assess the robustness of the deterministic estimate of cost-effectiveness when using transient elastography and multiparametric MRI in combination. The results of the random sampling show a standard deviation in the cost difference of £42 per test, suggesting that there is a 95% probability of this strategy remaining cost effective up to a price threshold of £547.

Threshold analysis

Setting the sensitivity and specificity of transient elastography at the lower and upper 95% confidence intervals gives break-even prices for multiparametric MRI when used in conjunction with transient elastography of £558 and £659 respectively. The price of multiparametric MRI therefore needs to be reduced if the performance of transient elastography is set to the most pessimistic levels. This is because transient elastography gives an increase in the proportion of positive results (from 41% to 53%) at this lower diagnostic accuracy. These patients then go on to multiparametric MRI and, as their transient elastography results are less accurate, they are more likely to be contradicted by multiparametric MRI. It is these patients with contradictory results who then go on for a liver biopsy. The model predicts that the percentage of the original cohort in this category would rise from 9.5% at the upper confidence level to 18% at the lower confidence level. Thus a more accurate transient elastography means fewer contradictory results, with fewer resultant biopsies. In the third treatment pathway of multiparametric MRI alone, the

corresponding break-even costs are £203 for the lower confidence interval, and £156 for the upper confidence interval.

Transient elastography and multiparametric MRI failure rate

Both transient elastography and multiparametric MRI can fail or give unreliable results. This is caused by patient characteristics, technical issues with the equipment, or operator inexperience. As NAFLD is associated with higher BMI, it might be expected that the failure rate for transient elastography in NAFLD patients would be higher than the 18.4% average reported in the Castéra et al. study.[25] However, with a lack of evidence to quantify any difference in average BMI of the two patient groups, and the subsequent effect on transient elastography failure rates, the figure of 18.4% was used in the model as a conservative estimate of the baseline failure rate. For multiparametric MRI, BMI is less of an issue, with failures related more to technical issues. Trials by the manufacturer have indicated a failure rate in the range of approximately 2.5% to 5% associated with the use of multiparametric MRI.

With these figures in mind, Tables 3a and 3b show an illustrative range of failure rates for transient elastography and multiparametric MRI, with the estimated break-even cost of multiparametric MRI when used as an adjunct to or replacement for transient elastography respectively.

Multiparametric MRI failure rate	Transient elastography failure rate			
	12%	18%	35%	50%
2.5%	£654	£638	£581	£543
5%	£638	£617	£567	£529
10%	£604	£585	£537	£501

Table 3a. Break-even cost of multiparametric MRI when used as an adjunct to transient elastography

Multiparametric MRI failure rate	Transient elastography failure rate			
	12%	18%	35%	50%
2.5%	£159	£221	£248	£306
5%	£148	£210	£237	£294
10%	£145	£187	£214	£271

Table 3b. Break-even cost of multiparametric MRI when used as a replacement for transient elastography

In the first scenario, as the failure rate of transient elastography increases, a higher proportion of patients move on to the second line diagnosis, with an associated increase in the total number of biopsies. With the extra cost of these biopsies the break-even price of multiparametric MRI decreases. In the second scenario, as the failure rate of transient elastography goes up, the break-even price of multiparametric MRI also goes up, as it is now replacing a decreasingly reliable

transient elastography. In both scenarios the break-even price of multiparametric MRI decreases with increased failures, as any extra failures at this stage mean extra liver biopsies.

Multiparametric MRI as the sole diagnostic test

For the third diagnostic pathway in Figure 1, multiparametric MRI replaces transient elastography as the first-line diagnostic test. In the modelled base-case for this scenario, as with transient elastography, patients receiving a positive diagnosis go on for a confirmatory biopsy to assess the nature and extent of any fibrosis. If it can be shown that multiparametric MRI is able to match the diagnostic accuracy of liver biopsy in this role, then there is the potential for it to replace biopsy as the definitive diagnosis of liver fibrosis. Incorporating this possibility into the model reduces the number of biopsies by 508 per 1000 patients, the expected number of positive multiparametric MRI tests; leaving biopsies for just the 5% of patients for whom the multiparametric MRI fails. Obviating the need for biopsies for those patients with positive multiparametric MRI, reduces the total testing costs to 14% of those in the first scenario of transient elastography backed up with liver biopsy. This means that the price of multiparametric MRI could remain cost effective up to a price of £672, if used as the sole diagnostic test replacing the combination of transient elastography and liver biopsy. Removing biopsy as the second line test inevitably has an effect on the overall diagnostic accuracy of this pathway, reducing the rate of correct diagnoses to 89%, with 78 cases of fibrosis remaining undiagnosed and 27 patients without fibrosis receiving a false positive test result.

DISCUSSION

This study proposes that the current NAFLD diagnostic pathway may become more cost-efficient with the inclusion of multiparametric MRI either as an adjunct to or replacement of transient elastography. The use of multiparametric MRI as an adjunct to transient elastography has the potential to reduce the number of liver biopsies by 66% while as a replacement would result in a decrease in the number of biopsies needed of 16%. A small drop in predicted diagnostic accuracy is predicted, but this is inevitable because some biopsies are avoided, and these are presumed, for our model, to be 100% accurate. Acquisition of further clinical evidence is required to confirm if the use of multiparametric MRI as an adjunct or replacement of transient elastography can result in cost savings for the NHS. The current study presents a preliminary decision analytic model, which can be adapted and developed as more evidence becomes available.

Given the increasing prevalence of obesity, it is possible that multiparametric MRI will become more useful considering transient elastography's unreliability and failed measurements associated with increased BMI.[25] Moreover, it has been observed

that the rate of un-interpretable results with transient elastography (due to fewer than 10 valid measurements) is 9.6%, a value that could be an under-estimation due to potential under-reporting.[28] The relationship between BMI and the prevalence of each stage of fibrosis has not been quantified, limiting any assessment of how the increased failure rate associated with obesity affects the diagnostic accuracy.

Controversy remains regarding the optimal cut-off values to diagnose advanced fibrosis using transient elastography as the cut-off values differ across aetiologies. This leads to variation in the interpretation of transient elastography results.[26] Initial findings suggest that multiparametric MRI can quantify the severity of liver disease.[27] This has implications in the monitoring and evaluation of liver disease progression. Currently, repeated liver biopsies are necessary to assess the stage liver disease. Both from a patient and payers' perspective, it would be preferable that progression of liver disease be evaluated by a non-invasive method capable of assessing the stage of the disease rather than by an invasive and more costly liver biopsy. Since increasing disease activity may also occur in patients with simple steatosis, all patients with NAFLD should undergo periodic disease progression assessment with lifestyle modification advice if appropriate.[9] The value of transient elastography in detecting early stages of liver disease is limited. Results of patients with low-stage grades of fibrosis (F<2) have been associated with significantly reduced reproducibility when compared to those of patients with marked fibrosis.[9, 30]

The current decision analytic model aims to compare only the diagnostic pathways for patients presenting with suspected NAFLD. It does not consider the consequences of any diagnosis, either correct or incorrect, or failures to diagnose, with subsequent short and long-term disease progression and associated treatment outcomes. Patients with suspected NAFLD whose tests are within the normal range with either transient elastography or multiparametric MRI should subsequently be re-tested within a period of one to two years in order to capture any possible disease progression. The model does not follow the progression of liver disease in individuals. Rather, it presumes that the prevalence of the various levels of fibrosis in the population presenting with suspected fatty liver disease, and associated diagnostic outcomes, remain broadly the same whether patients be new or returning. A more comprehensive model could be developed to consider the longer-term progression of liver disease in individuals combined with the treatment outcomes associated with the diagnoses. This would need considerably more evidence, and the HTA was unable to identify robust cost and quality-adjusted life year estimates or data on treatment effectiveness to inform such a model.[28] Future research should attempt to address the shortcomings of currently available evidence for this patient population. Other non-invasive techniques are emerging such as MR elastography, which uses a vibration source to generate low frequency mechanical waves in tissue.[31-33] The wave information is processed allowing the quantitative

assessment of the mechanical properties of tissue. The purpose of the current study was to evaluate the inclusion of multiparametric MRI in current diagnostic pathways for patients presenting with suspected NAFLD. MR elastography may be a valuable addition to currently used techniques and should be evaluated in further studies.

This model presumes that patients would not deviate from the best practice guidelines for diagnostic pathways.[14] However, in practice, diagnosis and treatment initiation is often solely based on clinical judgement without biopsy. A recent survey observed that fewer than 25% of participating specialists performed liver biopsies to diagnose NASH, which diverges from guidelines and may leave NASH under-diagnosed in gastroenterology and hepatology clinics.[34]

Based on current practice, the reference standard for this model was liver biopsy, which is still regarded as the reference for differentiating steatosis from non-alcoholic steatohepatitis, for staging hepatic fibrosis, and for identifying NAFLD in patients with other chronic liver disease.[35] However, this is an imperfect reference standard and has recently been considered that liver biopsy is not a suitable test for monitoring responses to therapy or for following disease progression.[36] A UK national audit found that samples were insufficient for diagnosis in 71 (2.04%) of 3472 cases.[37] Inadequate liver biopsies in which a focal lesion was present at imaging occurred in 82 (7.1%) of 1162 biopsies and in 37 (1.7%) of 2155 liver biopsies where a focal lesion was not present.[37] The risk of excessive bleeding is about 1 in 500 to 1 in 1,000 and the risk of death is about 1 in 10,000 to 1 in 12,000.[38] Although this risk is substantially lower than previous reports, it should be noted that both transient elastography and multiparametric MRI have not been associated with any serious side-effects. These aspects should be taken into account when modelling the long-term diagnostic pathways.

CONCLUSION

This study demonstrates that the inclusion of multiparametric MRI in the diagnostic pathway of NAFLD may lead to savings to the NHS if the model presumptions hold. Multiparametric MRI could be included either as an adjunct to or replacement of transient elastography, with both scenarios presenting savings compared to the current pathway to initial fatty liver diagnosis. In our model, the use of multiparametric MRI as an adjunct to transient elastography is predicted to more than halve the number of biopsies required. It is important to generate additional high quality clinical evidence and cost data to develop the model further, and test its predictions. Current results suggest investment in evidence generation would have value. If these studies show that multiparametric MRI is able to match the diagnostic accuracy of liver biopsy to quantify disease progression, then there is the potential for it to replace biopsy for the diagnosis of liver fibrosis, with significant cost savings to the healthcare provider.

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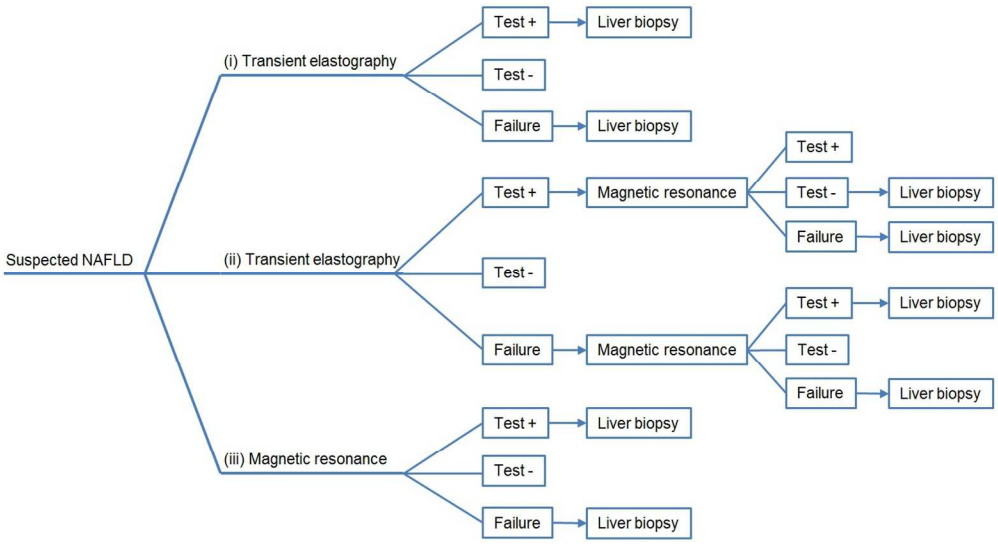

Decision analytic model of diagnostic pathways

391x211mm (96 x 96 DPI)

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

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

Section/item	Item No	Recommendation	Reported on page No/ line No
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.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
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.	3-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	4,5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	7
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.	N/A
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.	6, 7
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
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.	6, 7
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.	7
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.	5, 6
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	6, 7
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.	6, 7
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.	TABLE 1
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.	8 - 11
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	N/A

		of methodological assumptions (such as discount rate, study perspective).	
	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.	9, 10
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.	9, 10
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.	11-12
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.	13
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.	13

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

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A decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multi-parametric magnetic resonance imaging

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A decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multiparametric magnetic resonance imaging

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ABSTRACT

Objectives: The mortality associated with liver disease continues to increase despite the improvements implemented in the UK healthcare as does the prevalence of non-alcoholic fatty liver disease (NAFLD) given the escalating prevalence of obesity. The currently available methods to assess and monitor the stage of liver disease present several limitations. Recently, multiparametric magnetic resonance imaging (MRI) has been developed to address these limitations. The aim of this study is to develop a decision analytic model for patients with suspected NAFLD, to investigate the effect of adding multiparametric MRI to the diagnostic pathway.

Perspective: The model takes the perspective of the UK National Health Service (NHS) as the service provider.

Methods: A simple decision-tree model was developed to compare the costs associated with three diagnostic pathways for NAFLD that use non-invasive techniques. Firstly using transient elastography alone, secondly using multiparametric MRI as an adjunct to transient elastography, and thirdly, multiparametric MRI alone. The model was built to capture these clinical pathways, and used to compare the expected diagnostic outcomes and costs associated with each.

Results: The use of multiparametric MRI as an adjunct to transient elastography, while increasing screening costs, is predicted to reduce the number of liver biopsies required by about 66%. Used as the sole diagnostic scan, there remains an expected 16% reduction in the number of biopsies required. There is a small drop in the overall diagnostic accuracy, as in the current model liver biopsy is presumed to give a definitive diagnosis.

Conclusion: The inclusion of multiparametric MRI, either as an adjunct to or replacement of transient elastography, in the diagnostic pathway of NAFLD may lead to cost savings for the NHS if the model presumptions hold. Further high quality clinical evidence and cost data are required to test the model's predictions.

Strengths and limitations of this study

- This is the first study to evaluate the costs associated with the inclusion of a new method to assess liver disease in the diagnostic pathway of patients with suspected non-alcoholic fatty liver disease.
- Potential cost savings to the NHS have been identified by the use of multiparametric MRI as an adjunct or replacement of transient elastography if the model presumptions hold.
- The current decision analytic model compares only the diagnostic pathways; it does not consider the consequences of any diagnosis and does not follow the progression of liver disease in individuals.
- Additional high quality clinical evidence and cost data are necessary to further develop and test the model's predictions.

INTRODUCTION

Liver disease refers to any disorder of the liver that leads to a reduction of its functioning. There are several types of liver disease including sequelae of hepatitis, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). ALD and NAFLD have similar pathological spectra and disease may progress through simple hepatic steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma.[1, 2] The clinical differentiation between ALD and NAFLD is usually performed by taking a history of a patient's alcohol intake combined with laboratory and imaging examinations. Patients with non-alcoholic steatohepatitis (NASH) usually exhibit more advanced fatty degeneration of liver cells than those with alcoholic steatohepatitis and the inflammatory infiltrate in NASH is somewhat less pronounced than in alcoholic steatohepatitis.[2]

Improvements made in UK healthcare have resulted in a decrease of mortality rates for most health conditions, including heart disease, endocrine or metabolic disease, respiratory disease and diabetes.[3] Liver disease is the exception. The standardised mortality rate has increased by almost 500% since 1970 in patients younger than 65 years.[3] Liver disease accounts for 62,000 years of working life lost every year; only ischaemic heart disease (74,000 years) and self-harm (71,000 years) lead to a greater premature loss of life.[4]

Between 1988 and 2008, the prevalence of chronic liver disease caused by hepatitis B virus, hepatitis C virus, and alcoholic liver disease has remained stable.[5] During the same period, the prevalence of NAFLD increased from 5.51% to 11.01%.[5] It is expected that the prevalence of NAFLD will continue to increase given the escalating prevalence of obesity; with projections to the year 2030 estimating a 33% increase in obesity and a 130% increase in severe obesity.[6]

Fatty liver (i.e. simple steatosis) was believed to be a benign condition with no or minimal rate of progression. However, recent evidence suggests that a substantial proportion of patients (28-32%) with simple steatosis progress towards NASH and fibrosis within a three to four-year period.[7-9] In most patients NASH develops on a background of diabetes or impaired glucose tolerance in the long-term.[10] Progression to cirrhosis, hepatocellular carcinoma and increased mortality has been reported for patients with NASH.[11, 12]

It is important therefore, to detect fatty liver disease at its early stages before progression into NASH, a cirrhotic stage or liver cancer. The early stages of NAFLD can be managed and may regress if lifestyle advice is provided and followed. Weight reduction has been found to be associated with non-progressive disease.[9] The early detection of NAFLD is important to establish an effective course of treatment, and has the potential to reduce the economic burden of liver disease and save lives.[13] Recent EASL–EASD–EASO clinical practice guidelines have

recommended that all individuals with persistently abnormal liver enzymes or steatosis should be screened for NAFLD.[14]

Liver biopsy

Liver biopsy is currently considered as the reference standard for the diagnosis of liver disease. Liver biopsy is nevertheless imperfect when used to assess the extent of disease progression in terms of fibrotic transformation of liver tissue. This is because it allows examination of only a very small area of the liver, potentially missing the disease as changes within the liver can be patchy. In addition, there is variability in histological interpretation depending on the individual pathologist's experience.[15, 16] Liver biopsy is invasive and associated with a risk of haemorrhagic complications. It can also be painful and stressful for the patient as well as time consuming. It is a relatively costly procedure and has a low level of diagnostic performance for early stages of fibrosis.[17, 18] Liver biopsy may cause anxiety in patients, and has been found to be painful in up to 30% of cases.[19] A recent willingness to pay evaluation found that most patients (75%) who had undergone a liver biopsy (publicly funded in British Columbia) would be willing to self-pay for transient elastography (not publicly funded in British Columbia).[20] The majority of patients preferred the non-invasive transient elastography method, as it was associated with less discomfort during and after the scan, and no feelings of anxiety after the procedure was explained.[20] Only those patients with unknown liver disease were found to prefer liver biopsy. There is a need in the diagnostic and monitoring pathway for non-invasive methods to assess and monitor the stage of liver disease.

Transient elastography

Transient elastography is a non-invasive method to assess hepatic fibrosis using ultrasound to measure the velocity of an elastic shear wave transmitted through the liver and assess liver stiffness.[21] It is a painless test for which sedation is not required, it is significantly less expensive than liver biopsy, and it has not been associated with any adverse treatment-effects.[16] However, despite being widely used, the cut-off values of liver stiffness for the different stages of liver fibrosis are not well established.[22] Using transient elastography, significant variations in liver stiffness measurements related to operator and patient factors rather than to disease progression have been observed.[23] The variations in cut-off values and measurements limit the effectiveness of transient elastography for monitoring and assessing the progression of liver fibrosis.[23] In addition, transient elastography has a high failure rate, particularly among obese patients. The reported failure rates vary widely, ranging from 4.5% in a cohort of patients with chronic liver disease,[24] to 41% in a cohort of patients with BMI of 35 kg/m^2 or higher.[9] A five-year prospective study of 13,369 examinations of patients with suspected chronic liver disease reported an average failure rate for transient elastography of 18.4%.[25] The main

factors influencing reliability were limited operator experience and obesity, particularly increased waist circumference. Sub-group analysis in this study found the failure rate ranging from 12% (BMI < 25) to 53% (BMI > 40).[25] Failure rates for transient elastography are higher for obese patients as the ultrasound wave used by the probe can be strongly attenuated by fatty tissue.[26] This limitation is important as obese patients have an increased risk of liver disease progression.

Multiparametric magnetic resonance

Multiparametric magnetic resonance is a new non-invasive technique designed to diagnose liver fibrosis. It consists of software (Liver*MultiScan*) that enables the assessment of multiparametric liver data (i.e. fat, iron, and fibrosis) based on a magnetic resonance (MR) scan. The first study on this technology reported an average scan time of 23 minutes and demonstrated that multiparametric MRI can quantify hepatic fibrosis, iron, and steatosis.[27] Transverse abdominal T1 and T2* MR maps, corresponding to segment 8 of the liver are acquired.[27] The majority of percutaneous liver biopsies are taken from this area. Once the image is acquired, an operator defines a region of interest of the liver lobe, away from vascular and biliary structures. The image is analysed remotely, removing the need for interpretation by a radiologist, potentially reducing the time needed for scan results and costs. The software generates a report for the clinician, with analyses of fat, iron and fibrosis levels in the liver. Multiparametric MRI has been included as the only liver imaging test in the UK Biobank study.

Aim of the study

The aim of this study was to develop a preliminary decision analytic model of the diagnostic pathways for patients with suspected NAFLD using two non-invasive methods: (i) transient elastography and (ii) multiparametric magnetic resonance. Such a model could indicate the potential value of investment in further research and inform the design of such research.

METHODS

Modelling methodology

A simple decision-tree model was constructed in Excel to compare the costs associated with three diagnostic pathways for NAFLD that use non-invasive techniques. Firstly, using transient elastography alone, then using multiparametric MRI as an adjunct to transient elastography, and finally using multiparametric MRI alone (Figure 1). The chosen pathways were based on current clinical practice according to clinical advice. The model was built to capture these clinical pathways,

and used to compare the expected diagnostic outcomes and costs associated with each.

(Insert Figure 1 here)

For the base case model, it is presumed that the diagnostic pathways as set out in Figure 1 are followed exactly by all patients. In practice these pathways, and the decision whether to take a liver biopsy at any stage, may vary between individual patients depending on other indications or clinical opinion.

The first patient pathway uses transient elastography as the first-line non-invasive diagnosis. Patients whose test results are within the normal range are referred back to their general practitioner and no further immediate tests are carried out. Patients giving a positive test move on to the next stage in the diagnostic pathway, which in this case is a confirmatory liver biopsy. Patients for whom the test failed also move on to the next stage of liver biopsy.

In the second pathway, multiparametric MRI is introduced as a second line, non-invasive diagnostic tool for those patients for whom the transient elastography either gave a positive diagnosis or failed, and who would otherwise have had a liver biopsy at this stage. For those with a positive transient elastography, a further positive diagnosis with multiparametric MRI is considered as confirmatory with no further tests necessary, whereas a contradictory negative test or a failure results in a liver biopsy. For those patients for whom the initial transient elastography failed, multiparametric MRI becomes the first line diagnosis whereby test outcomes are treated as with transient elastography alone. That is, a normal result requires no immediate further action, a positive result would require a confirmatory biopsy, and a second failure would be followed by a diagnostic biopsy.

In the final pathway, multiparametric MRI replaces transient elastography as the first line diagnostic tool with test outcomes treated in the same way.

Model parameters

A hypothetical cohort of 1000 patients presenting with suspected NAFLD was modelled. Initial clinical suspicion would be based on laboratory findings and the absence of other causes of liver disease. The estimated prevalence for the successive stages of fibrosis in the cohort was taken from a recent Health Technology Assessment (HTA).[28] In their analysis, 48 studies were used to assess the sensitivity and specificity of a number of diagnostic tools at successive thresholds of liver fibrosis. Overall prevalence at each threshold was calculated from the populations in the included studies. The median prevalence (minimum–

maximum) of fibrosis stages F1–F4 in the studies identified, as well as additional model parameters, are presented in Table 1. The median prevalence at each threshold was taken to calculate prevalence for each level of fibrosis in the modelled population.

In the model, the sensitivity and specificity of transient elastography at each threshold, as calculated in the HTA, were used to predict the proportion of positive and negative test results. For multiparametric MRI, sensitivity and specificity for any level of fibrosis were taken from Banerjee et al.[27] For those in the modelled cohort with liver fibrosis, the relevant sensitivities of the tests were used to predict the rates for true positives and false negatives, while for those without fibrosis, the specificities were used to predict the rates of false positives and true negatives. Rates for test failures for multiparametric MRI were provided by the manufacturer.

Costs

The model takes the perspective of the UK National Health Service (NHS) as the service provider. The costs for transient elastography and liver biopsy were derived from the HTA report [28] and inflated from 2012 to 2014 prices using the Personal Social Services Research Unit inflator.[29] A price for the multiparametric MRI procedure is not currently available. For the base case analysis we presumed the cost of multiparametric MRI to be the same as transient elastography. Cost-effectiveness thresholds for multiparametric MRI were evaluated for each of the diagnostic pathways with this diagnosis option. Probabilistic sensitivity analysis was conducted using the sensitivity and specificity of transient elastography. Given the short modelling horizon of the diagnostic pathways, no costs were discounted.

Model parameter		Source
NAFLD prevalence		
Fibrosis stage	Median (minimum-maximum)	
F 1	0.588 (0.367-0.814)	Crossan et al. [28]
F 2	0.319 (0.119-0.526)	Crossan et al. [28]
F 3	0.186 (0.050-0.440)	Crossan et al. [28]
F 4	0.128 (0.039-0.907)	Crossan et al. [28]
Sensitivity of transient elastography for diagnosis of NAFLD		
Fibrosis stage	Summary sensitivity (95% CI)	
F ≥ 1	0.87 (0.81 to 0.92)	Crossan et al. [28]
F ≥ 2	0.79 (0.72 to 0.85)	Crossan et al. [28]
F ≥ 3	0.82 (0.74 to 0.88)	Crossan et al. [28]
F ≥ 4	0.96 (0.83 to 0.99)	Crossan et al. [28]
Specificity of transient elastography for diagnosis of NAFLD		
Fibrosis stage	Summary specificity (95% CI)	
F ≥ 1	0.76 (0.57 to 0.88)	Crossan et al. [28]
F ≥ 2	0.76 (0.71 to 0.80)	Crossan et al. [28]
F ≥ 3	0.84 (0.78 to 0.89)	Crossan et al. [28]
F ≥ 4	0.89 (0.85 to 0.92)	Crossan et al. [28]
Sensitivity of multiparametric MRI for diagnosis of NAFLD		
Any fibrosis	0.86	Banerjee et al. [27]
Specificity of multiparametric MRI for diagnosis of NAFLD		
Any fibrosis	0.93	Banerjee et al. [27]
Failure rates	Base case (range)	
Transient elastography	18.4% (12% to 50%)	Castéra et al. [25]
Multiparametric MRI	5% (2.5% to 10%)	Manufacturer data
Costs		
Transient elastography	£52.44	Crossan et al. [28]
Liver biopsy	£983.70	Crossan et al. [28]

Table 1. Summary of model inputs

RESULTS

Diagnostic pathway

Using transient elastography alone with the median values for sensitivity and specificity, the model suggests that for the cohort of 1000 patients with suspected NAFLD there would be 496 positive and 319 negative test results. With 184 failures, 680 patients would move to the next diagnostic level; which in this case is a liver biopsy. Based on the prevalence of fibrosis, and the specificity of transient elastography, 64 patients with fibrosis would continue undiagnosed, giving a diagnostic accuracy for this pathway of 93.6% if liver biopsy is presumed to give a definitive diagnosis. Introducing multiparametric MRI as a second line diagnostic tool before liver biopsy requires a further 680 multiparametric MRI tests for those patients thus indicated, but is predicted to more than halve the total number of liver biopsies required to 254. With the reduced number of biopsies, the overall diagnostic accuracy falls to 91.6%, with 78 patients with fibrosis remaining undiagnosed and 5 patients without fibrosis receiving an incorrect positive diagnosis. Using multiparametric MRI instead of transient elastography would be expected to yield 508 positive and 442 negative test results. With 50 failures, 558 liver biopsies would then be indicated. The diagnostic accuracy for this pathway is 92.2%, with 78 undiagnosed cases of fibrosis.

Cost analysis

For multiparametric MRI to be a cost-efficient addition in the diagnosis of NAFLD, any increase in costs associated with its use, either as an adjunct to or instead of transient elastography, needs to be compensated for by a reduction in the number of biopsies needed. As a reference point, if multiparametric MRI were to cost the same as transient elastography, *i.e.* £52.44, the results outlined above would give the cost outcomes as summarised in Table 2.

	Transient elastography		Transient elastography plus multiparametric MRI		Multiparametric MRI	
	Number	Cost	Number	Cost	Number	Cost
Transient elastography tests	1000	£52,440	1000	£52,440	0	£0
Multiparametric MRI tests	0	£0	680	£35,684	1000	£52,440
Liver biopsies	679	£669,374	254	£249,902	558	£548,702
Total cost	£721,819		£338,026		£601,142	

Table 2. Base case results

When using multiparametric MRI as an adjunct to transient elastography, the cost of the expected extra 680 tests is more than offset by the savings made by the

reduction in the number of biopsies required. When used instead of transient elastography, the cost of testing remains the same, and there is some reduction in the number of expected biopsies, due to a lower failure rate and better diagnostic accuracy (mainly a better selectivity resulting in a lower rate of false positives).

Threshold and sensitivity analysis

The expected cost savings to be made in the two scenarios that use multiparametric MRI suggest that there is an opportunity to increase the price. When used as a second line diagnosis after transient elastography, the use of multiparametric MRI remains cost effective up to £616 per test. This figure reflects the potential cost savings that could be made by performing these two types of scans before considering a biopsy. When used as the sole non-invasive diagnostic tool prior to liver biopsy, multiparametric MRI remains a cost-effective replacement for transient elastography up to a cost of £173 per test. This figure is lower than the previous threshold as in this scenario there is again just one scanning method used before a possible biopsy.

Probabilistic sensitivity analysis

The HTA report used the included studies to calculate the sensitivity and specificity of transient elastography, reporting mean values with 95% confidence intervals.[28] Probabilistic sampling was done on these distributions to assess the robustness of the deterministic estimate of cost-effectiveness when using transient elastography and multiparametric MRI in combination. The results of the random sampling show a standard deviation in the cost difference of £42 per test, suggesting that there is a 95% probability of this strategy remaining cost effective up to a price threshold of £547.

Threshold analysis

Setting the sensitivity and specificity of transient elastography at the lower and upper 95% confidence intervals gives break-even prices for multiparametric MRI when used in conjunction with transient elastography of £558 and £659 respectively. The price of multiparametric MRI therefore needs to be reduced if the performance of transient elastography is set to the most pessimistic levels. This is because transient elastography gives an increase in the proportion of positive results (from 41% to 53%) at this lower diagnostic accuracy. These patients then go on to multiparametric MRI and, as their transient elastography results are less accurate, they are more likely to be contradicted by multiparametric MRI. It is these patients with contradictory results who then go on for a liver biopsy. The model predicts that the percentage of the original cohort in this category would rise from 9.5% at the upper confidence level to 18% at the lower confidence level. Thus a more accurate transient elastography means fewer contradictory results, with fewer resultant biopsies. In the third treatment pathway of multiparametric MRI alone, the

corresponding break-even costs are £203 for the lower confidence interval, and £156 for the upper confidence interval.

Transient elastography and multiparametric MRI failure rate

Both transient elastography and multiparametric MRI can fail or give unreliable results. This is caused by patient characteristics, technical issues with the equipment, or operator inexperience. As NAFLD is associated with higher BMI, it might be expected that the failure rate for transient elastography in NAFLD patients would be higher than the 18.4% average reported in the Castéra et al. study.[25] However, with a lack of evidence to quantify any difference in average BMI of the two patient groups, and the subsequent effect on transient elastography failure rates, the figure of 18.4% was used in the model as a conservative estimate of the baseline failure rate. For multiparametric MRI, BMI is less of an issue, with failures related more to technical issues. Trials by the manufacturer have indicated a failure rate in the range of approximately 2.5% to 5% associated with the use of multiparametric MRI.

With these figures in mind, Tables 3a and 3b show an illustrative range of failure rates for transient elastography and multiparametric MRI, with the estimated break-even cost of multiparametric MRI when used as an adjunct to or replacement for transient elastography respectively.

Multiparametric MRI failure rate	Transient elastography failure rate			
	12%	18%	35%	50%
2.5%	£654	£638	£581	£543
5%	£638	£617	£567	£529
10%	£604	£585	£537	£501

Table 3a. Break-even cost of multiparametric MRI when used as an adjunct to transient elastography

Multiparametric MRI failure rate	Transient elastography failure rate			
	12%	18%	35%	50%
2.5%	£159	£221	£248	£306
5%	£148	£210	£237	£294
10%	£145	£187	£214	£271

Table 3b. Break-even cost of multiparametric MRI when used as a replacement for transient elastography

In the first scenario, as the failure rate of transient elastography increases, a higher proportion of patients move on to the second line diagnosis, with an associated increase in the total number of biopsies. With the extra cost of these biopsies the break-even price of multiparametric MRI decreases. In the second scenario, as the failure rate of transient elastography goes up, the break-even price of multiparametric MRI also goes up, as it is now replacing a decreasingly reliable

transient elastography. In both scenarios the break-even price of multiparametric MRI decreases with increased failures, as any extra failures at this stage mean extra liver biopsies.

Multiparametric MRI as the sole diagnostic test

For the third diagnostic pathway in Figure 1, multiparametric MRI replaces transient elastography as the first-line diagnostic test. In the modelled base-case for this scenario, as with transient elastography, patients receiving a positive diagnosis go on for a confirmatory biopsy to assess the nature and extent of any fibrosis. If it can be shown that multiparametric MRI is able to match the diagnostic accuracy of liver biopsy in this role, then there is the potential for it to replace biopsy as the definitive diagnosis of liver fibrosis. Incorporating this possibility into the model reduces the number of biopsies by 508 per 1000 patients, the expected number of positive multiparametric MRI tests; leaving biopsies for just the 5% of patients for whom the multiparametric MRI fails. Obviating the need for biopsies for those patients with positive multiparametric MRI, reduces the total testing costs to 14% of those in the first scenario of transient elastography backed up with liver biopsy. This means that the price of multiparametric MRI could remain cost effective up to a price of £672, if used as the sole diagnostic test replacing the combination of transient elastography and liver biopsy. Removing biopsy as the second line test inevitably has an effect on the overall diagnostic accuracy of this pathway, reducing the rate of correct diagnoses to 89%, with 78 cases of fibrosis remaining undiagnosed and 27 patients without fibrosis receiving a false positive test result.

DISCUSSION

This study proposes that the current NAFLD diagnostic pathway may become more cost-efficient with the inclusion of multiparametric MRI either as an adjunct to or replacement of transient elastography. The use of multiparametric MRI as an adjunct to transient elastography has the potential to reduce the number of liver biopsies by 66% while as a replacement would result in a decrease in the number of biopsies needed of 16%. A small drop in predicted diagnostic accuracy is predicted, but this is inevitable because some biopsies are avoided, and these are presumed, for our model, to be 100% accurate. Acquisition of further clinical evidence is required to confirm if the use of multiparametric MRI as an adjunct or replacement of transient elastography can result in cost savings for the NHS. The current study presents a preliminary decision analytic model, which can be adapted and developed as more evidence becomes available.

Given the increasing prevalence of obesity, it is possible that multiparametric MRI will become more useful considering transient elastography's unreliability and failed measurements associated with increased BMI.[25] Moreover, it has been observed

that the rate of un-interpretable results with transient elastography (due to fewer than 10 valid measurements) is 9.6%, a value that could be an under-estimation due to potential under-reporting.[28] The relationship between BMI and the prevalence of each stage of fibrosis has not been quantified, limiting any assessment of how the increased failure rate associated with obesity affects the diagnostic accuracy.

Controversy remains regarding the optimal cut-off values to diagnose advanced fibrosis using transient elastography as the cut-off values differ across aetiologies. This leads to variation in the interpretation of transient elastography results.[26] Initial findings suggest that multiparametric MRI can quantify the severity of liver disease.[27] This has implications in the monitoring and evaluation of liver disease progression. Currently, repeated liver biopsies are necessary to assess the stage liver disease. Both from a patient and payers' perspective, it would be preferable that progression of liver disease be evaluated by a non-invasive method capable of assessing the stage of the disease rather than by an invasive and more costly liver biopsy. Since increasing disease activity may also occur in patients with simple steatosis, all patients with NAFLD should undergo periodic disease progression assessment with lifestyle modification advice if appropriate.[9] The value of transient elastography in detecting early stages of liver disease is limited. Results of patients with low-stage grades of fibrosis (F<2) have been associated with significantly reduced reproducibility when compared to those of patients with marked fibrosis.[9, 30]

The current decision analytic model aims to compare only the diagnostic pathways for patients presenting with suspected NAFLD. It does not consider the consequences of any diagnosis, either correct or incorrect, or failures to diagnose, with subsequent short and long-term disease progression and associated treatment outcomes. Patients with suspected NAFLD whose tests are within the normal range with either transient elastography or multiparametric MRI should subsequently be re-tested within a period of one to two years in order to capture any possible disease progression. The model does not follow the progression of liver disease in individuals. Rather, it presumes that the prevalence of the various levels of fibrosis in the population presenting with suspected fatty liver disease, and associated diagnostic outcomes, remain broadly the same whether patients be new or returning. A more comprehensive model could be developed to consider the longer-term progression of liver disease in individuals combined with the treatment outcomes associated with the diagnoses. This would need considerably more evidence, and the HTA was unable to identify robust cost and quality-adjusted life year estimates or data on treatment effectiveness to inform such a model.[28] Future research should attempt to address the shortcomings of currently available evidence for this patient population. Other non-invasive techniques are emerging such as MR elastography, which uses a vibration source to generate low frequency mechanical waves in tissue.[31-33] The wave information is processed allowing the quantitative

assessment of the mechanical properties of tissue. The purpose of the current study was to evaluate the inclusion of multiparametric MRI in current diagnostic pathways for patients presenting with suspected NAFLD. MR elastography may be a valuable addition to currently used techniques and should be evaluated in further studies.

This model presumes that patients would not deviate from the best practice guidelines for diagnostic pathways.[14] However, in practice, diagnosis and treatment initiation is often solely based on clinical judgement without biopsy. A recent survey observed that fewer than 25% of participating specialists performed liver biopsies to diagnose NASH, which diverges from guidelines and may leave NASH under-diagnosed in gastroenterology and hepatology clinics.[34]

Based on current practice, the reference standard for this model was liver biopsy, which is still regarded as the reference for differentiating steatosis from non-alcoholic steatohepatitis, for staging hepatic fibrosis, and for identifying NAFLD in patients with other chronic liver disease.[35] However, this is an imperfect reference standard and has recently been considered that liver biopsy is not a suitable test for monitoring responses to therapy or for following disease progression.[36] A UK national audit found that samples were insufficient for diagnosis in 71 (2.04%) of 3472 cases.[37] Inadequate liver biopsies in which a focal lesion was present at imaging occurred in 82 (7.1%) of 1162 biopsies and in 37 (1.7%) of 2155 liver biopsies where a focal lesion was not present.[37] The risk of excessive bleeding is about 1 in 500 to 1 in 1,000 and the risk of death is about 1 in 10,000 to 1 in 12,000.[38] Although this risk is substantially lower than previous reports, it should be noted that both transient elastography and multiparametric MRI have not been associated with any serious side-effects. These aspects should be taken into account when modelling the long-term diagnostic pathways.

CONCLUSION

This study demonstrates that the inclusion of multiparametric MRI in the diagnostic pathway of NAFLD may lead to savings to the NHS if the model presumptions hold. Multiparametric MRI could be included either as an adjunct to or replacement of transient elastography, with both scenarios presenting savings compared to the current pathway to initial fatty liver diagnosis. In our model, the use of multiparametric MRI as an adjunct to transient elastography is predicted to more than halve the number of biopsies required. It is important to generate additional high quality clinical evidence and cost data to develop the model further, and test its predictions. Current results suggest investment in evidence generation would have value. If these studies show that multiparametric MRI is able to match the diagnostic accuracy of liver biopsy to quantify disease progression, then there is the potential for it to replace biopsy for the diagnosis of liver fibrosis, with significant cost savings to the healthcare provider.

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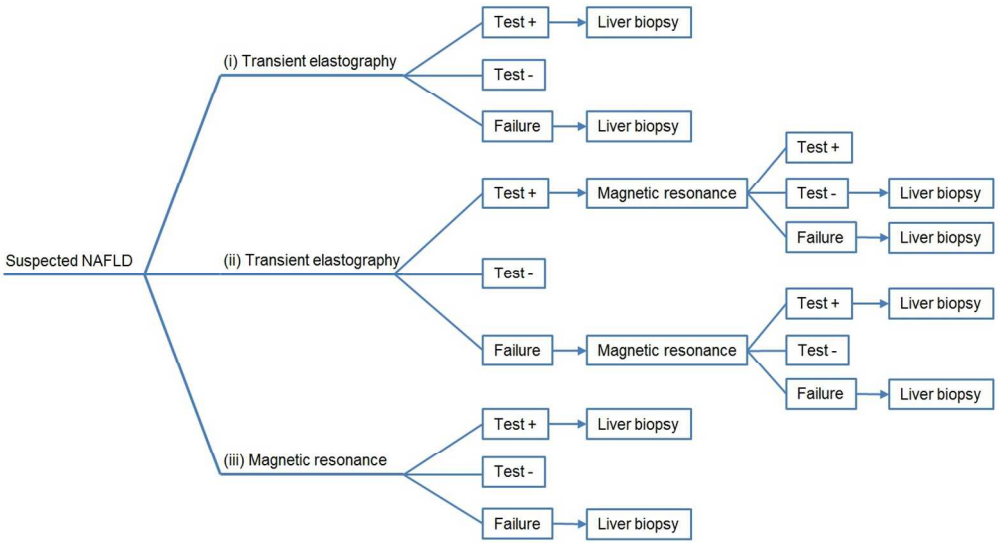

Decision analytic model of diagnostic pathways

391x211mm (96 x 96 DPI)

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

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

Section/item	Item No	Recommendation	Reported on page No/ line No
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.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
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.	3-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	4,5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	7
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.	N/A
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.	6, 7
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
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.	6, 7
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.	7
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.	5, 6
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	6, 7
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.	6, 7
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.	TABLE 1
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.	8 - 11
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	N/A

		of methodological assumptions (such as discount rate, study perspective).	
	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.	9, 10
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.	9, 10
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.	11-12
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.	13
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.	13

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

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

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