



# The cost-effectiveness of non-invasive liver tests for the detection of liver fibrosis in patients with suspected alcohol-related liver disease

Matt Stevenson,\* Myfanwy Lloyd Jones, Marsha Morgan  
\* m.d.stevenson@shef.ac.uk

## INTRODUCTION

Alcohol is the most common cause of liver disease in the Western world. Alcohol produces a spectrum of liver injury which includes fatty liver, alcoholic hepatitis, cirrhosis and hepatocellular carcinoma. Although patients with cirrhosis may remain symptom-free for several years, once complications develop survival is adversely affected. Currently, the reference standard for assessing liver damage is histological examination of a liver biopsy specimen: this allows, first, confirmation of a diagnosis of ALD; second, accurate staging of the degree of liver injury and third, exclusion of other or additional liver pathologies. This information is then used to determine prognosis and inform treatment decisions.

However, liver biopsy is associated with morbidity and mortality. In view of these difficulties, interest has arisen in the use of surrogate markers to assess the severity of liver injury. As liver fibrosis represents the final common outcome of chronic liver injury and is often progressive, evolving to cirrhosis, most of the non-invasive markers are in effect markers of this process. Much of the work in this field has centred on the evaluation of patients with chronic hepatitis C; there is little information on the use and potential cost-effectiveness of these markers in patients with ALD. The work undertaken evaluate the cost-effectiveness compared with liver biopsy, of four non-invasive liver tests (NILTs) specified by NICE, FibroTest, FibroMAX, the ELF test and FibroScan.

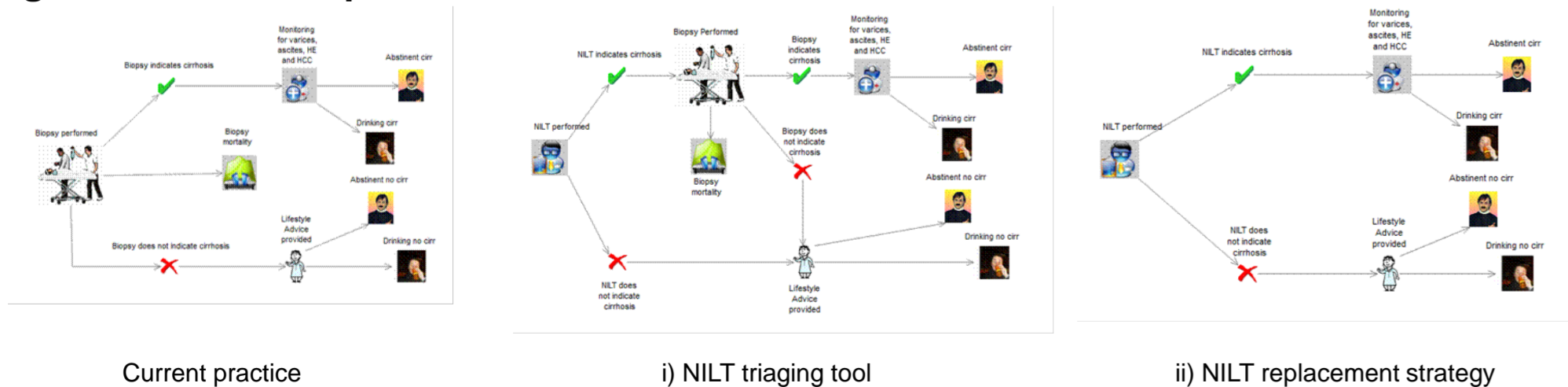
## METHODS

A systematic literature review was undertaken of the morbidity and mortality associated with liver biopsy (both percutaneous and transjugular). A review of health economic evaluations of the non-invasive tests and of liver disease was also completed. A simple decision tree model was constructed to provide an indicative value for the cost per QALY of each NILT.

The population simulated in the model comprises those patients a hepatologist might wish to biopsy. Certain patients would be biopsied as a matter of course, primarily those who would be candidates for treatment with corticosteroids. The proportion of the simulated population presenting to secondary and tertiary centres with cirrhosis was estimated by clinicians to be 35%.

In addition to optimal current practice, which is assumed to be that all patients would be biopsied, strategies were evaluated in which (i) a NILT would be used as a triaging tool, with only patients diagnosed as positive for cirrhosis receiving a biopsy, or (ii) a NILT would be used as a replacement test, with patient management determined solely on the diagnosis provided by the NILT. All patients would be given advice to reduce alcohol consumption, ideally to attain and maintain abstinence from alcohol; however, only those diagnosed with cirrhosis would be monitored, and treated where appropriate, for variceal haemorrhage, fluid retention, hepatic encephalopathy (HE) and hepatocellular carcinoma (HCC). In each model it was assumed that 20% of patients with precirrhotic liver damage at presentation who continued to misuse alcohol would eventually develop cirrhosis. For clarity, the possibility of incorrect diagnoses has not been shown in Figure 1.

Figure 1: The conceptual models



## MODEL POPULATION: Adverse events associated with liver biopsy

The systematic literature review estimated that the probability of mortality associated with a percutaneous liver biopsy is 0.09% with an additional risk of a serious adverse event of 0.72%; corresponding values for transjugular / transvenous biopsy are 0.18% and 1.27%.

## MODEL POPULATION: The accuracy of the NILTs

Table 1: Assumed NILT accuracy

NILT	NILT scenario	Data source	Patients (n)	Threshold	Biopsy: 100% sensitivity		Biopsy: 80% sensitivity Pessimistic		Biopsy: 80% sensitivity Optimistic	
					Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
ELF Test	1	Rosenberg, 2004	64	0.431	92.4%	97.4%	75.0%	93.8%	92.4%	97.4%
	2	Rosenberg, 2004	64	0.087	98.9%	18.4%	92.9%	3.1%	99.1%	43.8%
	3	Authors' estimate for cirrhotics only	-	0.431	96.0%	90.0%	78.0%	87.0%	95.0%	92.0%
FibroTest	1	Naveau, 2005	221	0.70	91.2%	86.9%	72.9%	85.3%	92.9%	97.4%
	2	Naveau, 2005	221	0.30	99.3%	50.3%	80.0%	44.1%	99.4%	56.6%
	3	Thabut, 2007	66	0.74	78.3%	78.6%	78.3%	25.0%	78.7%	91.7%
FibroScan	1	Müller 2010	101	11.5	98.1%	77.3%	81.3%	75.3%	98.5%	84.1%
	2	Janssens 2010	49	19.6	78.6%	75.9%	64.0%	70.8%	90.0%	82.7%
	3	Nahon, 2008	147	22.7	83.5%	83.6%	66.7%	76.6%	85.6%	99.1%

No data were found for FibroMAX. For the remaining NILTs the studies were small, with often conflicting results. For each NILT, three scenarios that were deemed plausible estimates of the accuracy were selected. Three scenarios were undertaken regarding the sensitivity of biopsy: (i) the sensitivity of the liver biopsy was 100%; (ii) the sensitivity of the liver biopsy was 80% and the NILTs failed to detect the cirrhosis (a pessimistic scenario); and (iii) the sensitivity of the liver biopsy was 80% and the NILTs detected cirrhosis but the results were incorrectly classified as false positives (an optimistic scenario). The biopsy specificity was assumed to be 100%.

## MODEL POPULATION. Cost and QALYs associated with each model endpoint

Table 2: Outcome Measures

Endpoint	Costs £	QALYs
True positives for cirrhosis: abstain from alcohol	27,400	9.410
True positives for cirrhosis: continue to misuse alcohol	37,400	3.764
False positives for cirrhosis: abstain from alcohol	20,500	11.066
False positives for cirrhosis: continue to misuse alcohol	20,500	11.066
True negatives for cirrhosis: abstain from alcohol	1,000	11.066
True negatives for cirrhosis: continue to misuse alcohol	3,000	11.066
False negatives for cirrhosis: abstain from alcohol	26,100	9.359
False negatives for cirrhosis: continue to misuse alcohol	36,100	3.744

These values were estimated to present a plausible representation of the costs and QALYs associated with the endpoints contained in the three models. Full details are provided in the forthcoming publication.

Additionally, prophylactic intervention for variceal haemorrhage, and potential subsequent treatment of variceal bleeds were estimated via a simple decision tree model. This model predicted that screening and providing prophylactic treatment for those with oesophageal varices who abstain from alcohol would gain 0.269 QALYs per person at a cost £1,708; for those who continued to misuse alcohol, the values were 0.635 QALYs at a cost of £1,194.

Biopsy-related mortality was associated with no further costs and no further QALYs.

## SCENARIOS UNDERTAKEN

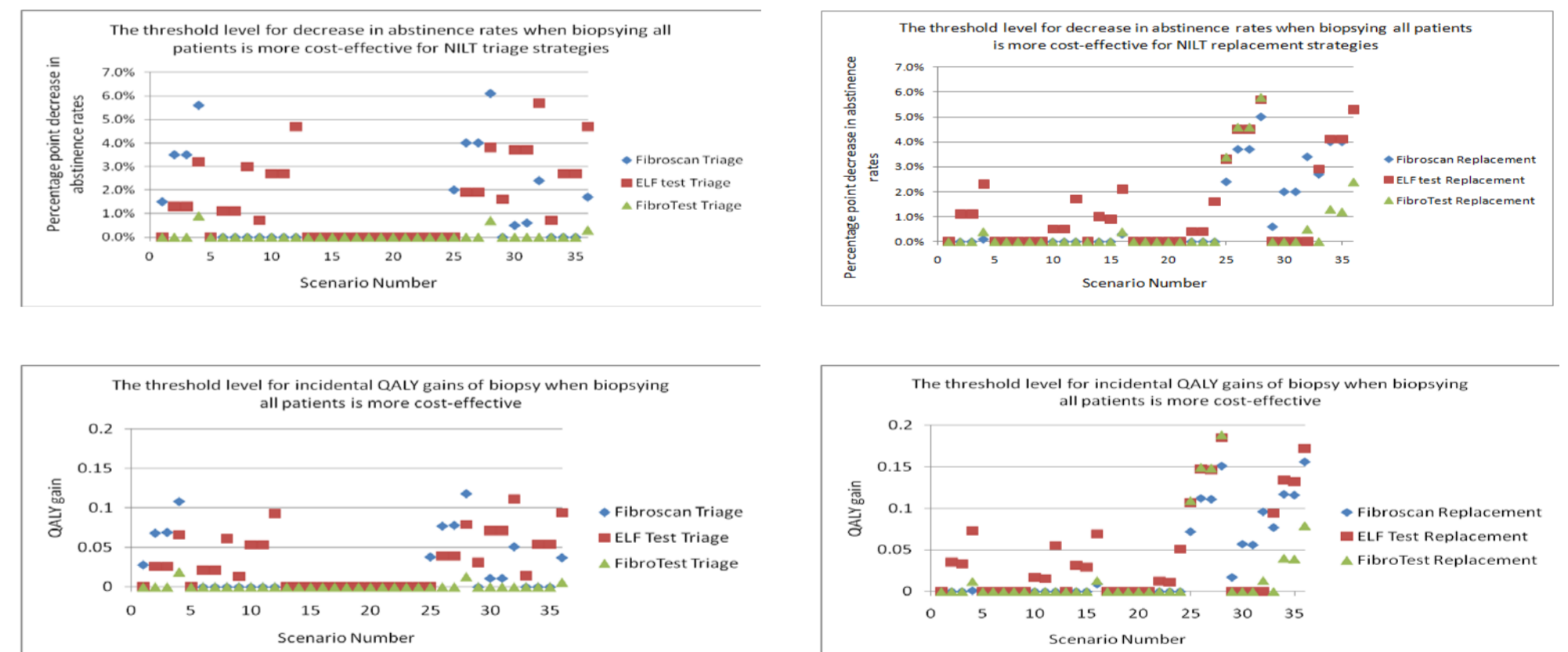
The results of the model were very sensitive to the level of abstinence from alcohol achieved and to any gains in QALYs due to a biopsy being performed. It is possible that the abstinence rates following diagnosis provided by a NILT could be lower than after biopsy, as the physician, and potentially the well-informed patient, might know that the NILTs have low specificity and do not provide information on the levels of fat and inflammation within the liver. It is also possible that a patient may derive benefit from a definitive diagnosis of their condition, particularly when alcohol misuse is assumed but denied, and access to appropriate treatment can be provided. However, no data were available to populate either parameter.

A series of threshold analyses was deemed to be most appropriate indicating what level of reduction in abstinence levels or what gain in QALYs due to a biopsy diagnosis was required for the option 'biopsying all patients' to be cost-effective, assuming a cost per QALY threshold of £20,000. Steps of 0.1 percentage points for decrease in abstinence rates and 0.001 QALY provided by a biopsy were used. This approach was preferred to a formal probabilistic sensitivity analysis, as this might have imparted greater certainty in the results than truly exist by estimating a single cost per QALY value.

Thirty-six scenarios were undertaken for each NILT and strategy (triage or replacement). These represented all combinations of biopsy sensitivity scenarios, NILT accuracy scenarios, liver biopsy method, and whether the patient was assigned a disutility of 0.2 QALYs due to anxiety associated with the biopsy procedure.

## RESULTS:

Figure 2: Threshold Results



## CONCLUSION

The data on which to make an informed judgement on whether the use of NILTs in diagnostic strategies for patients with suspected ALD is cost-effective were not identified. Further research is required to enable a robust decision to be made. Given current data, the possibility that the use of NILTs in order to reduce the number of biopsies undertaken would lead to a reduction in overall health cannot be discounted.

## FORTHCOMING PUBLICATION (which includes all references)

Stevenson M, Lloyd Jones M. Non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease. Health Technol Assess (In Press)



The University of Sheffield.