



## **Enhanced Liver Fibrosis Test (ELF) for evaluating liver fibrosis**

### **Target group**

- Patients with liver fibrosis caused by viral hepatitis, alcoholic liver disease and non-alcoholic fatty liver disease.

### **Technology description**

The Enhanced Liver Function test (ELF) is a non-invasive diagnostic test that uses a combination of serum markers to assess both the stage and the rate of progression of liver fibrosis. ELF is the first test to measure direct markers of liver fibrosis. Direct serum markers are proteins that reflect extracellular matrix metabolism/degradation produced as a result of the fibrogenic process. Indirect markers are measures of liver function based on commonly available laboratory tests (aspartate aminotransferase (AST), gamma-glutamyl-transpeptidase (GGT), bilirubin etc.), which are combined using algorithms.

The ELF test combines three direct serum markers; hyaluronic acid (HA), procollagen III amino terminal peptide (PIIINP) and tissue inhibitor of metalloproteinase 1 (TIMP-1) using an algorithm developed by the European Liver Fibrosis Group based on an international multi-centre cohort study in 1,021 patients<sup>1</sup>. The algorithm measures each of the markers by immunoassay to create an ELF score. Blood samples are collected in the clinic and analysis is performed at a central laboratory.

The company propose that in some situations serum markers could be used in place of liver biopsy (the current reference test) in the assessment of liver fibrosis, as well as in longitudinal monitoring and in assessing responses to interventions such as lifestyle modification or treatment. In all other situations serum markers would be used in conjunction with liver biopsy.

### **Innovation and/or advantages**

The most significant advantage of ELF is that more patients could be assessed at much more frequent intervals than compared with liver biopsy. ELF carries significantly reduced risk to the patient, incurs minimal pain and overcomes the sampling issues associated with liver biopsy (approximately 55% of 15mm biopsies can be misclassified as fibrosis is not evenly distributed throughout the liver).

### **Developer**

iQur Ltd (spin out company based at the University of Southampton) in collaboration with Siemens Medical Diagnostic Solutions (formerly Bayer Healthcare).

### **Availability, launch or marketing dates, and licensing plans:**

ELF was CE marked in May 2007. It is being marketed to the NHS, but currently is predominantly used for research purposes.

### **NHS or Government priority area:**

This topic relates to the:

- Hepatitis C Strategy for England.
- National Alcohol Strategy
- Obesity Strategy: Healthy Weight, Healthy Lives.

## Relevant guidance

### NICE Technology Appraisals

- Hepatitis B (chronic) – tenofovir disoproxil fumarate. Proposed 17<sup>th</sup> wave.
- Hepatitis B (chronic) – adefovir dipivoxil and pegylated interferon alpha-2a. 2006<sup>2</sup> (review date February 2009).
- Hepatitis C – peginterferon alfa and ribavirin. 2006<sup>3</sup> (review date being considered). This is an extension of Hepatitis C – pegylated interferons, ribavirin and alfa interferon. 2004.

### NICE Interventional Procedures

- Extracorporeal albumin dialysis for acute-on-chronic liver failure.
- Laparoscopic liver resection.
- Living-donor liver transplantation.
- Radiofrequency-assisted liver resection.
  
- Haute Autorité de Santé<sup>a</sup>. Guidelines for the diagnosis of uncomplicated cirrhosis. 2007<sup>4</sup>.
- SIGN. Management of hepatitis C. A national clinical guideline. 2006<sup>5</sup>.
- British Society for Gastroenterology. Guidelines on the use of liver biopsy in clinical practice. 2004<sup>6</sup>.

## Clinical need and burden of disease

### Hepatitis C

Liver fibrosis is associated with significant morbidity and mortality. The major cause is hepatitis C. Hepatitis C virus (HCV) causes chronic hepatitis in about 80% of those infected. Recent estimates suggest that approximately 200,000 to 500,000 people are infected with HCV in England and Wales<sup>3</sup>. In 2005 the Department of Health estimated that only 47,000 people with HCV infection had been diagnosed and only 7,000 had been treated.

People infected with HCV are often asymptomatic, but about 20% will develop overt hepatitis. The rate of progression of the disease is slow but variable, usually taking about 20–50 years from the time of infection. About 30% of those who are infected develop cirrhosis within 20–30 years, and a small percentage of these people are at a high risk of developing hepatocellular carcinoma. A third may never progress to cirrhosis or will not progress for at least 50 years.

### Hepatitis B

The Department of Health estimates that about 180,000 people in the UK have chronic hepatitis B<sup>2</sup>. There are about 7,700 new cases of chronic hepatitis B each year. Of these, around 300 people were infected within the UK; the remainder (mainly immigrants to the UK) were infected abroad, generally in areas of high prevalence where the virus is frequently transmitted from mother to child.

People with active chronic hepatitis B are at increased risk of liver cirrhosis and primary liver cancer.

### Alcoholic Liver Disease (ALD)

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<sup>a</sup> French National Authority for Health.

In 2005, 4,160 people died in England and Wales from alcoholic liver disease, an increase of 37% since 1999<sup>7</sup>. The process is initially silent, but when liver disease has developed it presents as an acute illness with a 25-50% immediate mortality rate. In England, around 39,180 people are admitted to hospital with alcoholic liver disease each year.

There are three main stages of ALD: minimal change, or fatty liver; alcoholic hepatitis; and cirrhosis. Severe alcoholic steatohepatitis (ASH) is the major complication of advanced ALD and has a high mortality even when treated with corticosteroids.

#### Non-alcoholic fatty liver disease (NAFLD)

The prevalence of NAFLD is approximately 20-30% in western countries<sup>8</sup>, which would approximate to between 10.7 – 16.1M people in England and Wales. It covers a number of conditions, including non-alcoholic steatohepatitis (NASH). Severe obesity, type 2 diabetes, hypertension and/or dyslipidaemia are major risk factors. NASH is usually benign and very slowly progressive but can result in the development of fibrosis in up to 40% of patients, or cirrhosis in 5-10% of patients.

### **Existing comparators and treatments**

#### Invasive

The reference standard for the assessment of fibrosis in chronic liver conditions is currently a liver biopsy. Liver biopsies, which are associated with a degree of sampling error, are generally performed under local anaesthesia and require a short hospital stay. Liver biopsy is an invasive technique with a risk of serious adverse events due to bleeding and other complications and therefore should only be performed if the benefits outweigh the risks (in terms of altering treatment or disease outcome).

#### Non-Invasive

An alternative to liver biopsy is the non-invasive prediction of the severity of liver disease using combinations of clinical and biochemical parameters. Recent SIGN guidelines<sup>5</sup> recommend that:

- biochemical markers should not be used as an alternative to liver biopsy for the staging of intermediate grades of fibrosis
- biochemical tests may be used as an alternative to liver biopsy to diagnose cirrhosis or to direct screening for complications of fibrosis.

Transient elastography (FibroScan – EchoSens) is another non-invasive diagnostic technique currently in the early stages of diffusion that uses ultrasound to measure the stiffness (or elasticity) of the hepatic parenchyma.

Guidelines from France recommend that once a patient has been referred to a specialist, and a firm diagnosis cannot be made from the clinical and biological observations, a liver biopsy or a non-invasive test has to be carried out<sup>4</sup>. The recommended first-line test for the chronic untreated hepatitis C patient with no comorbidities is a non-invasive procedure (either FibroTest<sup>b</sup> or FibroScan)<sup>4</sup>.

#### Hepatitis C

The decision to treat a person with hepatitis C does not depend on a liver biopsy, however the clinician may recommend a biopsy for other reasons or if a strategy of watchful waiting is chosen.

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<sup>b</sup> FibroTest measures fibrosis by combining the variables of age and gender with 5 indirect serum biomarkers.

### Hepatitis B

The hepatitis B surface antibody (anti-HBs) is the most common test for hepatitis B. Other tests detect the presence of viral antigens. Liver biopsy is an accepted part of the diagnosis and management of patients with chronic hepatitis B and can be used for grading fibrosis and inflammation.

### Alcoholic Liver Disease (ALD)

If ALD is suspected, liver function tests, blood counts, and hepatitis serology are performed. No specific test exists for alcoholic liver disease. The role and timing of liver biopsy in patients with suspected ALD remains uncertain. In patients with evidence of liver damage and a history of alcohol excess, a liver biopsy is helpful in determining the degree of liver damage.

### Non-alcoholic fatty liver disease (NAFLD)

NAFLD is often asymptomatic, and may be identified through abnormal LFTs or by abdominal ultrasound. The role of liver biopsy for this indication is not clearly established. Histology remains the gold standard for making the important distinction between simple steatosis (which is generally non-progressive and readily reversible) and NASH.

## **Efficacy and safety**

### Diagnostic performance of ELF markers<sup>1</sup>:

The table below sets out the sensitivity and specificity for ELF compared to liver biopsy and histology for different patient groups. Note however that ELF scores have been grouped into dichotomous variables (0-2: no/mild versus 3-4: moderate/severe), rather than separate scores.

Disease	AUC <sup>c</sup>	Score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NAFLD	0.870	0.375	89%	96%	80%	98%
		0.462	78%	98%	87%	96%
ALD	0.944	0.087	100%	16.7%	75%	100%
		0.431	93.3%	100%	100%	85.7%
HCV	0.773	0.067	90%	31%	27.5%	92.3%
		0.564	30%	99%	89.5%	83.3%

An additional study in patients with NAFLD has recently reported that ELF detected severe, moderate and no fibrosis at AUCs of 0.90, 0.82 and 0.76 respectively<sup>9</sup>.

## **Estimated cost and cost impact**

The cost of the ELF test is currently unknown.

In patients younger than 70 without complications the cost of an inpatient biopsy (HRG code G05) is £710 (elective) and £2,213 (non-elective)<sup>10</sup>.

## **Potential or intended impact – speculative**

### **Patients**

- |   |  |   |
|---|--|---|
| <input type="checkbox"/> Reduced morbidity                            | <input type="checkbox"/> Reduced mortality or increased survival | <input checked="" type="checkbox"/> Improved quality of life for patients and/or carers |
| <input checked="" type="checkbox"/> Quicker, earlier or more accurate | <input type="checkbox"/> Other:                                  | <input type="checkbox"/> None identified  |

<sup>c</sup> The closer the area under the receiver operating characteristic curve (AUC) value is to 1, the more accurate the test.

diagnosis or identification of disease

### Services

- |   |  |  |
|---|--|--|
| <input checked="" type="checkbox"/> Increased use | <input type="checkbox"/> Service reorganisation required | <input checked="" type="checkbox"/> Staff or training required |
| <input type="checkbox"/> Decreased use            | <input type="checkbox"/> Other:                          | <input type="checkbox"/> None identified                       |

### Costs

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> Increased unit cost compared to alternative | <input checked="" type="checkbox"/> Increased costs: more patients coming for treatment<br>- ELF permits assessments to be performed in many more patients than alternative means would realistically allow. | <input type="checkbox"/> Increased costs: capital investment needed |
| <input type="checkbox"/> New costs:                                  | <input checked="" type="checkbox"/> Savings: Could replace the need for some biopsies.   | <input type="checkbox"/> Other:                                     |

### References

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- <sup>4</sup> Fontaine H, Petitprez K, Roudot-Thoraval F and Trinchet J-C. Guidelines for the diagnosis of uncomplicated cirrhosis. *Gastroenterol Clin Biol* 2007;31:504-509.
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- <sup>10</sup> NHS Tariff. 2007-2008.

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