

Transient elastography (FibroScan) for evaluating liver fibrosis

Target group

- All patients with chronic liver disease in particular those with suspected liver fibrosis associated with hepatitis B and C, non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH) and non-alcoholic fatty liver disease (NAFLD).

Technology description

FibroScan is an active medical diagnostic aid, which makes non-invasive, painless and immediate measurements of the stiffness (or elasticity) of the hepatic parenchyma. A FibroScan test is conducted by placing a probe in an intercostal space over the patient's liver triggering a shear wave, which is tracked through the liver using the ultrasound element of the probe (FibroScan is currently of limited use in obese patients). FibroScan can be performed by trained medical or paramedical staff. Each test typically takes less than 15 minutes in total. The acquisition speed is very high and the acquisitions are therefore not biased by cardiac or respiratory movements as they are with ultrasound imaging. FibroScan can be used as an initial screening tool to reduce the number of patients requiring liver biopsy and also to measure ongoing response to treatment. In some patients the initial screening results may be sufficiently well-defined to provide a confident assessment of the patient's stage of liver fibrosis.

Innovation and/or advantages

Unlike with a needle biopsy of the liver no anaesthetic is needed with FibroScan and the patient can be discharged immediately. No special infrastructure or specialist consumables are required for FibroScan. Whilst many patients will still require a biopsy, the company believe that a reduction in biopsies of between 40 to 60% may be observed when FibroScan is employed.

The most significant advantage of FibroScan may be that many more patients could be assessed at much more frequent intervals compared with liver biopsies^a. The patient cohorts who would most benefit may be those with recurrent disease (whatever the aetiology) post-transplant and those with viral hepatitis^a.

Developer

EchoSens (Artemis Medical Ltd. are the UK distributor).

Availability, launch or marketing dates, and licensing plans:

CE marked. Currently installed in 12 NHS hospitals. Most of the systems in use within the NHS have been funded by either pharmaceutical companies and/or charity donations. The company predict that the initial uptake is likely to be in the major hepatology centres (approximately 35 systems). The second phase requirement would be into DGHs with gastroenterology departments. Expert opinion suggests that national guidelines regarding the use of FibroScan are needed.

NHS or Government priority area:

No NHS or government priority area was identified.

^a Expert opinion

Relevant guidance

- The Centre for Evidence-based Purchasing (CEP) is currently conducting an evidence review of FibroScan (publication date not known).

NICE Technology Appraisals

- Hepatitis B (chronic) – tenofovir disoproxil fumarate. Proposed 17th wave.
- Hepatitis B (chronic) – adefovir dipivoxil and pegylated interferon alpha-2a. 2006¹ (review date February 2009).
- Hepatitis C – peginterferon alfa and ribavirin. 2006² (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^b. Guidelines for the diagnosis of uncomplicated cirrhosis. 2007³.
- SIGN. Management of hepatitis C. A national clinical guideline. 2006⁴.
- British Society for Gastroenterology. Guidelines on the use of liver biopsy in clinical practice. 2004⁵.
- The Canadian Agency for Drugs and Technologies in Health (CADTH). Transient elastography (FibroScan) for non-invasive assessment of liver fibrosis. 2006⁶.
Stated that the diagnostic performance of FibroScan is good for identifying severe fibrosis or cirrhosis, but is less accurate for milder presentations. FibroScan is a promising technology, but large multi-centre trials comparing a range of emerging non-invasive fibrosis staging technologies are required.
- The Australia and New Zealand Horizon Scanning Network (ANZHSN). MR and transient elastography for the non-invasive assessment of liver fibrosis. 2006⁷.
Stated that elastography (magnetic resonance and transient) appears to be a reliable technique for diagnosing severe liver fibrosis. For conditions such as viral hepatitis however, antiviral therapy should ideally begin in the early stages of fibrosis. Given the low quality of evidence outlining the ability of elastography to detect mild or moderate fibrosis, it is recommended that the technology be archived^c.

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 Wales². 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

^b French National Authority for Health.

^c The company have received enquiries from Australia regarding FibroScan.

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 B¹. 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)

In 2005, 4,160 people died in England and Wales from alcoholic liver disease, an increase of 37% since 1999⁸. 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 countries⁹, 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

The gold 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).

An alternative for liver biopsy is the non-invasive prediction of the severity of liver disease using combinations of clinical and biochemical parameters. Recent SIGN guidelines⁴ 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.

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 out³. The recommended first-line test for the chronic untreated hepatitis C patient with no comorbidities is a non-invasive procedure (either FibroTest^d or FibroScan)³.

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.

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 liver function tests (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

There are numerous published trials, conference presentations, ongoing trials and several non-systematic reviews pertaining to FibroScan. Two systematic reviews were identified, which included 4 studies¹⁰ and 9 studies¹¹ respectively (see table for details of the latter review) – these reviews had 3 studies in common.

Title	Ultrasound-based transient elastography for the detection of hepatic fibrosis
Status	Published 2007 ¹¹
Design	Systematic review and meta-analysis
Description of study	Studies reporting accuracy of ultrasound-based transient elastography compared with liver biopsy were identified through (i) search of PubMed (MEDLINE), EMBASE, Cochrane Library, Database of Abstracts of Reviews of Effects, Web of Science, SCOPUS, American College of Physicians Journal Club, Google Scholar databases from database inception to January 2007, and (ii) review of abstracts and proceedings from the American Association for the Study of Liver Disease, European Association for the Study of the Liver, and Digestive Disease Week annual meetings between 2003-2006. N=9 studies (2,083 patients) identified.
Primary outcome	Diagnostic test performance of ultrasound-based transient elastography for the detection of cirrhosis (stage IV fibrosis) vs no cirrhosis (stages 0-III fibrosis) compared

^d FibroTest combines the variables of age and gender with 5 biomarkers. Reported to ACTS in January 2004 for Hepatitis C and updated for chronic liver conditions in July 2005 (ACTS decided the topic did not meet the selection criteria).

	with the reference standard of liver biopsy.
Secondary outcomes	Diagnostic test performance of ultrasound-based transient elastography for detecting stages II-IV fibrosis vs stage 0-I fibrosis.
Key results	For patients with stage IV fibrosis (9 studies), the pooled estimates for sensitivity were 87% (95% CI, 84%-90%), specificity 91% (95% CI, 89%-92%), positive likelihood ratio 11.7 (95% CI, 7.9-17.1), and negative likelihood ratio 0.14 (95% CI, 0.10-0.20). For patients with stages II-IV fibrosis (7 studies), the pooled estimates for sensitivity were 70% (95% CI, 67%-73%), specificity 84% (95% CI, 80%-88%), positive likelihood ratio 4.2 (95% CI, 2.4-7.2), and negative likelihood ratio 0.31 (95% CI, 0.23-0.43). Diagnostic threshold (or cut-off value) bias was identified as an important cause of heterogeneity for pooled results in both patient groups.

Estimated cost and cost impact

FibroScan has an initial capital cost of £49,950 (+VAT) plus an annual maintenance cost of £3,000 (+VAT) from year 2 onwards. The cost per test will vary depending on the usage of the machine. The more the machine is used the lower the cost per patient.

In patients younger than 70 without complications the cost for an inpatient biopsy (HRG code G05) is £710 (elective spell) and £2,213 (non-elective spell)¹².

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 diagnosis or identification of disease | <input type="checkbox"/> Other: | <input type="checkbox"/> None identified |

Services

- | | | |
|---|--|--|
| <input checked="" type="checkbox"/> Increased use | <input type="checkbox"/> Service reorganisation required | <input checked="" type="checkbox"/> Staff or training required – FibroScan assessments generally undertaken by existing staff. Training is typically 3-4 hrs per operator. |
| <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 type="checkbox"/> Increased costs: more patients coming for treatment | <input checked="" type="checkbox"/> Increased costs: capital investment needed |
| <input type="checkbox"/> New costs: | <input checked="" type="checkbox"/> Savings: FibroScan permits assessments to be performed in many more patients than alternative means would realistically allow. Once purchased, the cost per patient is primarily only that of the operator | <input type="checkbox"/> Other: |

References

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²National Institute for Health and Clinical Excellence. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. Technology appraisal TA106. August 2006.

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- ¹¹ Talwalker JA, Kurtz DM, Schoenleber SJ et al. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology* 2007;5:1214-1220.
- ¹² NHS Tariff. 2007-2008.

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The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, Edgbaston, Birmingham, B15 2TT, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.pcpoh.bham.ac.uk/publichealth/horizon