Healthcare Improvement Scotland | SHTG Advice on health technologies

Advice Statement 010-18
July 2018

Advice Statement

What is the most accurate and cost-effective direct test (ELF test™, hyaluronic acid, P3NP, Fibroscan® or ARFI elastography) for detecting and staging liver fibrosis and/or cirrhosis in patients with diagnosed or suspected non-alcoholic fatty liver disease, alcohol-related liver disease, or viral hepatitis?

Advice for NHSScotland

Due to the limited comparative evidence available for the direct liver fibrosis tests of interest, SHTG is unable to provide advice to NHSScotland on the most accurate and cost-effective test for detecting and staging liver fibrosis. Further research is needed to inform advice on the diagnostic value of direct serum biomarkers compared with each other and with Fibroscan® and ARFI elastography.

The two direct imaging tests (Fibroscan® and acoustic radiation force impulse (ARFI) elastography) had similar diagnostic accuracy for detecting significant fibrosis and cirrhosis, and are likely to be the most clinically useful direct liver fibrosis tests in secondary care settings. None of the identified studies evaluated fibrosis tests in a primary care setting.

The most cost-effective liver fibrosis testing option varied by underlying liver disease, was subject to uncertainty and sensitive to changes in model parameters or assumptions.

NHSScotland is required to consider the Scottish Health Technologies Group (SHTG) advice.

Why is SHTG looking at this topic?

Direct tests are potentially useful for detecting liver fibrosis and cirrhosis but there is currently a lack of consistency in access to, and use of, these tests in Scotland. Identifying the most accurate and cost-effective test(s) for diagnosing liver fibrosis would facilitate early intervention to prevent disease progression, increase fibrosis diagnosis and help ensure that patients receive the most appropriate care. The topic was prioritised for inclusion on the SHTG programme following a topic referral from the Scottish Clinical Biochemistry Managed Diagnostic Network.

Evidence Note 82 (July 2018) was produced by Healthcare Improvement Scotland in response to this request.

Background

Patients with non-alcoholic fatty liver disease (NAFLD), alcohol-related liver disease or viral hepatitis are at risk of developing liver fibrosis and cirrhosis. Liver fibrosis is a progressive condition resulting in scarring of the liver and loss of liver function. Cirrhosis is a final irreversible stage in the progression of liver fibrosis.

Fibrosis is categorised by the METAVIR scoring system as none/mild, significant, advanced, or cirrhosis. Non-invasive tests help diagnose liver fibrosis and cirrhosis without patients needing to have a liver biopsy (the reference standard for diagnosing liver fibrosis). These tests can be divided into:

- **Direct tests**
  - ***serum biomarkers*** – enhanced liver fibrosis (ELF) test™, serum hyaluronic acid, N-terminal propeptide type III procollagen (P3NP)
  - ***imaging*** – transient elastography (Fibroscan®), acoustic radiation force impulse (ARFI) elastography, and
- **Indirect tests** – fibrosis-4 (FIB4) score, aspartate transaminase: alanine transaminase (AST:ALT) ratio, AST:platelet ratio index (APRI) score, NAFLD fibrosis score.

Indirect tests use algorithms based on routine liver blood tests and patient characteristics, such as age and weight, to determine the likelihood of fibrosis and cirrhosis. Direct tests measure biological changes in the blood (biomarkers) or liver tissue stiffness (imaging) that occur as a result of the fibrosis process. Therefore direct tests are potentially more accurate for diagnosing liver fibrosis and cirrhosis.

Clinical effectiveness

- The best quality and greatest quantity of evidence related to Fibroscan® and ARFI elastography. There was variation and lack of reporting of threshold values used to define stages of fibrosis in many of the identified studies.
- A UK HTA presented diagnostic accuracy meta-analysis including the direct tests of interest and using liver biopsy as the reference standard. In the HTA the sensitivity of direct tests of interest ranged from 70% to 93% for detecting all stages of fibrosis and cirrhosis. Specificity ranged from 63% to 92%.
- No studies were identified that compared serum biomarkers with ARFI elastography, the P3NP biomarker with any other test, or serum biomarkers with each other.
- Diagnostic accuracy results from studies comparing direct fibrosis tests with each other are summarised in the following table:

Fibrosis stage	Direct fibrosis tests being compared: Fibroscan® (95% CI)	ARFI elastography (95% CI)	Conclusion
Significant	Sens. 0.74 (0.66 to 0.80) Spec. 0.83 (0.75 to 0.89)	Sens. 0.78 (0.72 to 0.83) Spec. 0.84 (0.75 to 0.90)	Based on a meta-analysis of 13 studies (n=1,163) Fibroscan® and ARFI elastography had similar diagnostic accuracy for the detection of significant fibrosis and cirrhosis.
Cirrhosis	Sens. 0.87 (0.79 to 0.92) Spec. 0.87 (0.81 to 0.91)	Sens. 0.89 (0.80 to 0.94) Spec. 0.87 (0.82 to 0.91)	
	Fibroscan® (95% CI)	**ELF test™ (95% CI)**	
Cirrhosis	Sens. 0.82 (0.75 to 0.88) Spec. 0.89 (0.86 to 0.92)	Sens. 0.78 (0.70 to 0.85) Spec. 0.64 (0.59 to 0.69)	Based on a meta-analysis of four studies (n=612) Fibroscan® was slightly more sensitive and more specific than the ELF test™ for detecting cirrhosis.
Significant	Sens. 0.71 (0.58 to 0.83) Spec. 0.92 (0.81 to 0.98)	Sens. 0.83 (0.64 to 0.94) Spec. 0.56 (0.40 to 0.72)	In a prospective diagnostic study (n=107) Fibroscan® was less sensitive and more specific than the ELF test™ for detecting significant and advanced fibrosis.
Advanced	Sens. 0.80 (0.59 to 0.93) Spec. 0.79 (0.69 to 0.87)	Sens. 0.83 (0.52 to 0.98) Spec. 0.70 (0.56 to 0.81)	
	Fibroscan® (95% CI)	**Hyaluronic acid (95% CI)**	
Cirrhosis	Sens. 0.92 Spec. 0.88	Sens. 0.72 Spec. 0.79	In a prospective diagnostic study (n=404) Fibroscan® had higher sensitivity and specificity for detection of cirrhosis compared with serum hyaluronic acid ($p<0.05$).

Sens = sensitivity; Spec = specificity; 95% CI = 95% confidence interval.

- In comparisons of direct tests with indirect fibrosis tests:
  - The ELF test™ was more sensitive but less specific than the indirect APRI and FIB4 scores for detection of significant fibrosis.
  - Fibroscan® had higher sensitivity than the indirect APRI and FIB4 scores for detection of fibrosis and cirrhosis.

Safety

- In the studies considered, no adverse events were identified relating to the use of non-invasive liver fibrosis tests.

Cost effectiveness

- Cost effectiveness of a wide range of liver fibrosis tests was assessed in the UK HTA that informed the clinical effectiveness section, with economic modelling for each aetiology separately.
- The tests of interest to NHSScotland were extracted from the HTA analysis and incremental costs, benefits and ICERs re-calculated in a restricted analysis. This restricted analysis indicated the following tests/strategies were the most attractive for each aetiology:
    - Hepatitis B ($HBeAg^+$): testing with hyaluronic acid resulted in 11.66 QALYs gained per patient at a total cost of £79,084, while test/treat no-one resulted in 9.64 QALYs at a cost of £37,831.
    - Hepatitis B ($HBeAg^-$): treating everyone without testing offered the highest health benefit (10.92 QALYs) for a cost of £96,525, while test/treat no-one was the second best strategy offering 8.83 QALYs for a cost of £37,579.
    - Hepatitis C: treat all without testing – ICER £8,573 per QALY vs. ARFI elastography.
    - Alcohol-related liver disease: Fibroscan® provided 9.02 QALYs at an overall cost of £20,009, whereas treating everyone without testing offered 9.50 QALYs for a cost of £31,004.
    - NAFLD (incremental cost per correct diagnosis): ARFI elastography offered the highest rate of true positives at an additional cost of £8,600 per case identified. The NAFLD fibrosis score (high cut-off) offered the highest rate of true negatives at an additional cost of £183 per case identified.
    - Cirrhosis irrespective of aetiology: ELF test™ – ICER £10,333/QALY vs Fibroscan®.
- The above tests may not be the same ones reported as the cost-effective option in the full HTA analysis which included a wider range of tests. All analyses were subject to uncertainty and sensitive to changes in parameters and model assumptions.

Patient social aspects

- The evidence examined did not encompass patient experience of non-invasive liver fibrosis testing. Patients may however prefer to avoid invasive tests such as liver biopsy.

Context (includes organisational issues)

- The ELF test™ is not currently used for routine testing in Scotland and may only be available to NHS boards with Siemens Healthcare Ltd as a supplier of clinical chemistry equipment. Hyaluronic acid is only used in NHS Lothian and P3NP is only used in NHS Tayside.
- Fibroscan® is available in the majority of Scottish hospitals. The availability of ARFI elastography in Scotland is unclear but may be an option on existing ultrasound machines.
- Fibroscan® and ARFI elastography are currently restricted to secondary care. However, mobile Fibroscan® devices are available from the manufacturer that could be used in a community setting.
- An 'intelligent LFTs' pilot project in NHS Tayside is being considered for national roll-out: GPs request blood tests for patients with abnormal liver function and no clear diagnosis; hospital laboratories automatically perform further tests to determine disease aetiology and inform the GP. Direct fibrosis tests may help target this system by more accurately identifying patients with fibrosis or cirrhosis.

Further research

Prospective diagnostic cohort studies are needed to inform use of direct fibrosis tests in NHSScotland. These studies should recruit patients with liver disease of different aetiologies, directly compare the ELF test™, hyaluronic acid, P3NP, Fibroscan® and ARFI elastography with each other, and report diagnostic accuracy, patient outcomes, and/ patient experiences and preferences.

Advice context

No part of this advice may be used without the whole of the advice being quoted in full. This advice represents the view of the SHTG at the date noted.

It is provided to inform NHS boards in Scotland when determining the place of health technologies for local use. The content of this Advice Statement was based upon the evidence and factors available at the time of publication. An international evidence base is reviewed and thus its generalisability to NHSScotland should be considered by those using this advice to plan services. It is acknowledged that the evidence constitutes only one of the sources needed for decision making and planning in NHSScotland. Readers are asked to consider that new trials and technologies may have emerged since first publication and the evidence presented may no longer be current. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgment in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

SHTG Advice Statements will be considered for review if new evidence becomes available which is likely to materially change the advice. Stakeholders may submit a request, highlighting new evidence to shtg.hcis@nhs.net

Acknowledgements

SHTG would like to thank the following individuals and organisations who provided comments on the draft Advice Statement:

- Sara Jenks, Consultant in Metabolic Medicine, NHS Lothian
- Alastair MacGilchrist, Consultant Hepatologist, Royal Infirmary of Edinburgh
- Judi Rhys, Chief Executive, British Liver Trust
- Prof Peter Hayes, Professor of Hepatology, University of Edinburgh
- Ian Godber, Lead Clinician, Scottish Clinical Biochemistry Managed Diagnostic Network
- Sarah Smith, Co-Founder, Liver4Life
- Prof John F Dillon, Consultant Hepatologist, Professor of Hepatology and Gastroenterology, University of Dundee
- Prof Philip Newsome, Consultant Hepatologist, University of Birmingham
- Miriam Brazzelli, Senior Research Fellow, Health Services Research Unit, University of Aberdeen

Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by the SHTG's Evidence Review Committee. However, reviewers had no role in authorship or editorial control and the views expressed are those of SHTG. Details of SHTG membership are available on the Healthcare Improvement Scotland *website*.

Chair
Scottish Health Technologies Group

NICE has accredited the process used by Healthcare Improvement Scotland to produce its evidence review products. Accreditation is valid for 5 years from January 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation