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1. Title of the project

Non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease

2. Name of Assessment Team and project lead

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3. Plain English Summary

Excess alcohol consumption is associated with alcoholic liver disease (ALD): alcoholic fatty liver (steatosis), alcoholic hepatitis, or alcoholic cirrhosis.[1] Steatosis, which usually asymptomatic, is reversible if alcohol consumption is stopped or significantly reduced.[1] Alcoholic hepatitis involves more severe liver damage.[2] Some patients are asymptomatic, but many suffer abdominal symptoms, and others present with acute alcoholic hepatitis characterised by jaundice, fever, liver failure, or bleeding.[1] In alcoholic cirrhosis, scar tissue (fibrosis) prevents the liver from working properly;[1] despite this, some people with early-stage alcoholic cirrhosis have no symptoms.[2] People with alcoholic cirrhosis are at increased risk of liver cancer.[1]

People who drink more than 10 units of alcohol daily will eventually develop steatosis; 10%-35% will develop alcoholic hepatitis, and approximately 10% will develop cirrhosis.[3] Some develop both cirrhosis and alcoholic hepatitis;[4] over 60% of these patients die within four years of diagnosis.[2] Abstinence from alcohol greatly improves survival in people with ALD.[1]

Patients with ALD come to medical attention in a number of ways. Many are identified following routine liver function tests, others when they report relatively mild abdominal symptoms. Some present with more severe symptoms caused by advanced liver disease.[3] Yet others present voluntarily for detoxification, require treatment for alcohol-related injuries, or present with alcoholic damage to other organs.[3] Liver biopsy may be used to confirm the diagnosis of ALD and provide information about the degree of fibrosis.[3,5] As an invasive procedure, it carries a risk of morbidity and mortality, particularly in patients with alcoholic hepatitis and cirrhosis.[3] Moreover, there is no high-quality evidence for its accuracy,[5] and therefore current draft guidance recommends that it is used only when confirmation of a diagnosis of acute alcoholic hepatitis is needed to inform specific treatment decisions.[5]

The key element of treatment for patients with ALD is long-term abstinence from alcohol. Other elements aim to prevent disease progression and manage complications. These include lifestyle changes (reducing smoking and obesity), nutritional therapy,[2] and therapies to treat specific complications of ALD.[3] Liver transplantation may be offered in extreme cases.[3]

At least 7,000 new cases of cirrhosis are diagnosed in the UK each year,[6] and in 2007 4,580 people in England and Wales died from ALD.[7] Around 80% of all cases of liver cirrhosis seen in district general hospitals in the UK are due to alcohol,[3] and many people in England and Wales consume alcohol at levels which put them at risk of ALD. In 2007, 24.2% of adults in England reported hazardous or harmful patterns of alcohol consumption.[8] Directly comparable figures are not available for Wales.[9]

The aim of this review is to systematically evaluate and appraise the potential clinical and cost effectiveness of using non-invasive liver assessment tools in patients who might otherwise be candidates for biopsy or referral to specialist care.

4. Decision problem

4.1 Purpose of the decision to be made

The aim of the assessment is to answer the following research question: Will using non-invasive liver assessment tools in patients with suspected alcohol-related liver fibrosis who might otherwise be candidates for biopsy or referral to specialist care reduce the number of referrals or biopsies and improve the health outcomes and quality of life of those patients?

4.2 Clear definition of the intervention

Four interventions are considered in this assessment: three are composite blood tests, and the fourth is a specialised scan.

The Enhanced Liver Fibrosis (ELF) test (iQur Ltd) is a blood test which uses an algorithm combining three biomarkers (hyaluronic acid, procollagen III amino terminal peptide and tissue inhibitor of metalloproteinase) to assess the stage and rate of progression of liver fibrosis. The

biomarkers are direct markers of extracellular matrix metabolism/degradation indicative of liver fibrosis. A higher concentration of the individual biomarkers leads to a higher ELF score, and therefore it is more likely there is more severe fibrosis. It is proposed that the ELF test can be used for the baseline determination of liver fibrosis. The ELF test is CE marked.

FibroTest and FibroMax (BioPredictive) are both proprietary algorithms of markers based on blood tests to assess the stage of liver fibrosis. FibroTest uses alpha-2 macroglobulin, a direct marker of extracellular matrix metabolism/degradation, and four indirect markers (apolipoprotein A1, haptoglobin, bilirubin, and gamma-glutamyl-transpeptidase). FibroMax adds to FibroTest additional markers for steatosis and alcohol related disease: these additional markers include ALT, AST, glucose, height and weight. Neither FibroTest nor FibroMax are CE marked, but there are CE marked kits for assessing the appropriate components.

FibroScan (EchoSens) is a device which uses transient elastography to assess liver stiffness, which is correlated with the degree of fibrosis. It consists of a specialised probe, an ultrasound and elastography system, and specialised software. The probe is placed on the skin over the liver, and generates a mechanical pulse which sends a shear wave through the liver. Liver stiffness is calculated from the velocity of the wave, which is measured by ultrasound. FibroScan is CE marked.

4.3 Place of the intervention in the treatment pathway(s)

The assessment will investigate the effect of using any of the four interventions in patients with suspected alcohol-related liver fibrosis who might otherwise be referred for biopsy or specialist care on the basis of their clinical history and physical examination and/or standard liver function tests. If data and resources allow, the effectiveness of tests in combination will also be assessed.

4.4 Relevant comparators

Referral to specialty care or biopsy based on clinical suspicion of liver fibrosis based on symptoms and/or liver function test results.

4.5 Populations and relevant subgroups

Patients with suspected liver fibrosis related to alcohol consumption. If time permits, consideration will be given to the subgroup of patients with suspected liver fibrosis who have hepatitis C in addition to high alcohol consumption.

4.6 Key factors to be addressed

The review will aim to:

- Investigate by systematic review the diagnostic accuracy of each of the four interventions in patients with suspected alcohol-related liver fibrosis

- Investigate by systematic review the impact of the four interventions on health and quality of life outcomes in patients with suspected alcohol-related liver fibrosis
- Estimate the potential benefits and harms arising from altered treatment based on the results of the four interventions
- Estimate the incremental cost effectiveness of providing routine testing using one of the four interventions to all patients newly diagnosed with suspected alcohol-related liver fibrosis who might otherwise be referred for biopsy or specialist care on the basis of the clinical history and physical examination and/or standard liver function tests.

5. Report methods for synthesis of evidence of clinical effectiveness

Systematic reviews of the evidence for diagnostic accuracy and health and quality of life outcomes will be undertaken; these will be informed by the general principles recommended in the PRISMA (formerly QUOROM) statement.[10] Evidence of diagnostic accuracy will be sought from studies which compare any of the four interventions with detected pathology or other diagnostic tools. Sensitivity (the proportion of true positives) and specificity (the proportion of true negatives) will be assessed.

In addition to the formal systematic review, the manufacturers may provide unpublished and confidential data, which would be analysed to provide further information on test characteristics.

The description of studies below covers studies that would provide direct comparative evidence for outcomes of interest. The Assessment Team recognizes that such studies are unlikely to exist and that indirect evidence will be needed to fill in the data requirements of the model. These data will be sought as the model design becomes apparent using the appropriate criteria. The same sources will apply.

5.1 Population

- Inclusion criteria: Patients with suspected liver fibrosis related to alcohol consumption.
- Exclusion criteria: Liver dysfunction attributed to other possible aetiologies. However, if time and evidence permit, consideration will be given to patients with suspected liver fibrosis related to alcohol consumption who also have hepatitis C.

5.2 Interventions

- Enhanced Liver Fibrosis (ELF) blood test
- FibroTest blood test
- FibroMax blood test
- FibroScan (transient elastography)

5.3 Comparators

Referral to specialty care or biopsy based on clinical suspicion of liver fibrosis based on symptoms and/or liver function test results.

5.4 Outcomes

- Diagnostic test accuracy
- Number of patients requiring referral to secondary care
- Number of patients requiring liver biopsy
- Number of patients giving up alcohol, or significantly reducing alcohol consumption
- Long-term patient outcomes (disease progression, complications related to liver disease, need for liver transplantation, mortality)
- Adverse effects of testing
- Health-related quality of life

5.5 Study design

- Inclusion criteria: for the review of clinical effectiveness the best available level of evidence will be included, with priority given to controlled studies if available. However, this criterion will be relaxed for the consideration of adverse events, for which observational studies may be included even if controlled studies are available.
- Exclusion criteria: studies will be excluded if they do not meet the inclusion criteria, appear to be methodologically unsound, or do not report results in the necessary detail. The following will also be excluded:
    - Animal models
    - Preclinical and biological studies
    - Narrative reviews, editorials and opinions
    - Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.

5.6 Search strategy

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers.

The electronic databases to be searched will include MEDLINE; Medline in Process; EMBASE; the Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register. A draft Medline search strategy is included in Appendix 1.

All citations will be imported into Reference Manager software and screened for inclusion on the basis of the inclusion/exclusion criteria listed above. Screening will be done in three stages,

sifting first by title, then by abstract, and finally by full text, excluding at each step studies which do not satisfy the inclusion/exclusion criteria.

5.7 Data extraction strategy

Data will be extracted by one researcher using a standardised data extraction form. Any studies which give rise to uncertainty will be reviewed by a second researcher, and any disagreements will be resolved by discussion, with involvement of a third researcher where necessary.

5.8 Quality assessment strategy

The nature of the quality assessment which will be undertaken will depend on the types of studies identified, but will be undertaken using appropriate and established tools (eg the QUADAS checklist for studies of diagnostic accuracy[11]).

5.9 Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to provide pooled estimates of test accuracy, and of patient outcomes.

5.10 Methods for estimating quality of life

In order to reflect the chronic nature of the disease, the time horizon of the analysis will be a patient's lifetime. The perspective will be that of the National Health Services and Personal Social Services. Both cost and QALY will be discounted at 3.5% as recommended by NICE.

6. Report methods for synthesising evidence of cost effectiveness

A systematic review of the existing literature studying the cost effectiveness of non-invasive diagnostic assessment tools for the detection of liver fibrosis will be undertaken.

6.1 Identifying and systematically reviewing published cost effectiveness studies

Studies relating to cost effectiveness will be identified using an economic search filter which will be integrated into the search strategy detailed in Section 5.6. This economic search filter is presented in Appendix 1.

6.2 Evaluation of costs and cost effectiveness

The quality of identified economic literature will be assessed using a combination of key components of the British Medical Journal checklist for economic evaluations[12] together with the Eddy checklist on mathematical models[13] (see Appendix 2).

6.3 Development of a health economic model

A *de novo* economic evaluation of the cost effectiveness of the use of each of the four interventions will be conducted. A model will be developed to identify whether the routine testing of all patients with one (or if resources allow multiple) non-invasive diagnostic test(s)

who are suspected of having alcohol-related liver disease and who would be referred for a liver biopsy is a cost effective use of resources.

The primary outcome from the model will be an estimate of the incremental cost per additional quality-adjusted life year (QALY) gained associated with the use of non-invasive diagnostic tests in the assessment of alcohol-related liver disease. A lifetime time horizon will be used in order to reflect the chronic effects of alcohol-related liver disease and potential mortality. The perspective used will be that of the UK National Health Service and Personal Social Services. Costs and QALYs will be discounted at 3.5% as recommended in the NICE reference case.[14] Modelling assumptions will be taken from the literature, supplemented by clinical expert opinion where required.

The development of the model is likely to be an iterative process. A conceptual model will be developed in conjunction with clinical experts to capture the current pathway of care for patients with suspected alcohol liver disease, and furthermore, how this pathway would change should non-invasive diagnostic tests become available for routine use. The conceptual model will indicate the data requirements which will be sought both from the published literature and within commercial in confidence data held by the manufacturers. The model is likely to evolve following discussions with project stakeholders and the Diagnostics Advisory Committee, and according to the availability of data.

Ideally, health related quality of life evidence will be available directly from the review literature. In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model. In addition to the reviewed literature, national sources (e.g. NHS reference costs, national unit costs,[15] British National Formulary) will be used to estimate resource use and costs for use in the economic model.

It is anticipated that there may be limited evidence for some of the parameters that will be included in the economic model. Therefore, the uncertainty around the parameter estimates will be modelled to take this into account. The uncertainty in the input parameters will be propagated through the model using PSA to characterise uncertainty in the outputs. Results will include the presentation of a cost effectiveness acceptability curve and the reporting of the expected value of perfect information.[16] If resources allow, the cost effectiveness of collecting further information will be explicitly explored using Expected Value of Partial Perfect Information[17] or the Expected Value of Sample Information techniques[18] which the team have experience of undertaking.[19,20]

7. Handling information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the Assessment Team in a timely manner. Data arriving after this date will not be considered. Data which meet the inclusion criteria for the review will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data taken from a company submission will be underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets) presented to the Diagnostics Advisory Committee only. In the version of the report released to manufacturers and other stakeholders, commercial in confidence data will be blacked out, thus ensuring confidentiality.

8. Competing interests of authors

None.

9. Timetable/milestones

The dates in this section are dependent on NICE's agreement to hold three Committee meetings (in May, September and November 2010) to discuss the pilot topic.

Milestone	**Date to be completed**
Draft protocol	11 December 2009
Final protocol	22 December 2009
Progress report	Weekly meetings
Draft assessment report to NICE for Committee consideration	7th May 2010
Presentation of draft assessment report, including model, to Diagnostics Advisory Committee (1st meeting)	28th May 2010
Final assessment report to NICE for circulation to stakeholders	10 weeks before 2nd Committee meeting (i.e. early – mid July 2010)
Stakeholder comments to NICE	July – August 2010
2nd Diagnostics Advisory Committee meeting	Late September 2010
3rd Diagnostics Advisory Committee meeting	Late November 2010 (8 weeks after 2nd Committee meeting)

10. Appendices

Appendix 1: Draft Medline search strategy and economic search filter

OVID Medline or Medline in Process

1. (enhanced adj liver adj fibrosis).tw.
2. (elf adj test$).tw.
3. (elf and diagnos$).tw.
4. (elf and (fibros*s or cirrhos*s).tw.
5. elf.tw.
6. exp liver cirrhosis/ or exp liver diseases, alcoholic/
7. 5 and 6
8. 1 or 2 or 3 or 4 or 7
9. fibrotest.tw.
10. fibrosure.tw.
11. fibromax.tw.
12. ashtest.tw.
13. fibroscan.tw.
14. (transient adj elastograph$).tw.
15. (elastograph$ and liver).tw.
16. or/9 to 15
17. exp liver cirrhosis/ or exp liver diseases, alcoholic/
18. (fibros*s or cirrhos*s).tw.
19. 17 or 18
20. Biological Markers/
21. biomarker$.tw.
22. (marker$ and (biologic$ or biochemical or serum or direct or indirect)).tw.
23. Algorithms/
24. algorithm$.tw.
25. (composite and blood).tw.
26. or/20-25
27. 19 and 26
28. Hyaluronic Acid/
29. ((hyaluronic adj acid) or (hyalauronate or hyaluronan).tw.
30. 28 or 29
31. ((procollagen or piiinp or p3np or ppcp)).tw.
32. ((tissue and inhibitor and metalloproteinase$) or timps).tw.
33. 30 and 31 and 32
34. 30 or 31 or 32
35. 34 and 19
36. Alpha-Macroglobulins/
37. ((alpha and macroglobulin$) or (alpha adj 2m)).tw.
38. or/36-37
39. ((apolipoprotein$ adj a1) or apoa1).tw.
40. Haptoglobins/
41. haptoglobin$.tw.
42. 40 or 41
43. (bilirubin$ or hematoidin$).tw.

44. (gamma adj glutamyl adj transpeptidase$).tw.
45. (gamma adj glutamyltransferase$).tw.
46. ((gamma adj gt) or ggt or ggtp).tw.
47. or/44-46
48. 38 and 39 and 42 and 43 and 47
49. 38 or 39 or 42 or 43 or 47
50. 49 and 19
51. ((alanine adj aminotransferase$) or aminotransaminase$).tw.
52. (serum adj glutamic adj pyruvic adj transaminase).tw.
53. sgpt.tw
54. or/51-53
55. (aspartate adj (aminotransferase$ or aminotransaminase$)).tw.
56. (serum adj glutamic adj oxaloacetic adj transaminase$).tw.
57. sgot.tw
58. or/55-57
59. 38 and 39 and 42 and 43 and 47 and 54 and 58
60. 38 or 39 or 42 or 43 or 47 or 54 or 58
61. 60 and 19
62. exp "Sensitivity and Specificity"/
63. sensitivity.tw.
64. specificity.tw.
65. ((pre-test or pretest) adj probability).tw.
66. post-test probability.tw.
67. predictive value$.tw.
68. likelihood ratio$.tw.
69. or/62-68
70. 27 and 69
71. 35 and 69
72. 50 and 69
73. 61 and 69
74. or/70-73
75. iqur.tw.
76. biopredictive.tw.
77. echosens.tw.
78. or/75-77
79. 8 or 16 or 33 or 48 or 74 or 78

Econometric search filter (OVID Medline) to follow from the above searches

1. exp "costs and cost analysis"/
2. economics/
3. exp economics, hospital/
4. exp economics, medical/
5. economics, nursing/
6. exp models, economic/
7. economics, pharmaceutical/
8. exp "fees and charges"/
9. exp budgets/
10. budget$.tw
11. ec.fs

12. cost$.ti
13. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab
14. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti
15. (price$ or pricing$).tw
16. (financial or finance or finances or financed).tw
17. (fee or fees).tw
18. (value adj2 (money or monetary)).tw
19. quality-adjusted life years/
20. (qaly or qalys).af.
21. (quality adjusted life year or quality adjusted life years).af.
22. or/1-21
23. 22 and 79 (above).

Appendix 2: Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluations[21] together with the Eddy checklist on mathematical models employed in technology assessments[13]

Reference ID		
Title		
Authors		
Year		
Modelling assessments should include:		**Yes/No**
1	A statement of the problem;	
2	A discussion of the need for modelling vs. alternative methodologies	
3	A description of the relevant factors and outcomes;	
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. *Note: n=number of health states within sub-model*	
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence;	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data;	
7	A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis;	
8	The results derived from applying the model for the base case;	
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.	
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect;	
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity.	
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results;	
13	A description of research in progress that could yield new data that could alter the results of the analysis	

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