D.19 Monitoring for liver disease

Item	Details
Issue in the scope	Surveillance for cystic-fibrosis related liver disease and prevention of progression.
Review questions in the scope	What is the effectiveness of ultrasound scanning to detect clinically important cystic-fibrosis-related liver disease?
Review questions in the protocol	• 1. What is the diagnostic accuracy of tests to detect/ strategies to detect early and late CF liver disease? • 2. What is the diagnostic and prognostic value of different strategies to detect CF liver disease and predict progression (including progression to cirrhosis and portal hypertension with (out) oesophageal varices)?
Objective	Diagnosis of CF liver disease is based on radiological methods (e.g. ultrasound scanning), biochemical tests, clinical methods (presence or absence of hepatosplenomegaly) and histological assessment. More recently liver stiffness testing using transient elastography has been developed although its use in CF patients is not well established. The estimated prevalence of hepatic fibrosis and liver disease is proposed to be between 26%-45% in patients with CF. Clinical presentation with hepatomegaly and/or splenomegaly is usually around 10 years of age. Progression of disease is from focal hepatic biliary fibrosis to development of cirrhosis and then portal hypertension with or without oesophageal varices. Early detection of hepatic injury and fibrosis allows treatment to be started (e.g. URSO). The gold standard test is a liver biopsy but in practice this is rarely performed (it is invasive, may miss focal lesions and has associated risks e.g. with respect to general anaesthesia or infection). Other gold standard tests are CT scanning and MRI scanning, however, although these investigations are not invasive, they are expensive and not routinely performed. More recently, definitions of liver disease have come into practice using recommendations based on the tests performed at clinical review e.g. CF liver disease is diagnosed if on at least 2 consecutive examinations spanning a one year period, two of the following conditions are met: • Hepatomegaly (liver span>2cm below the costal margin on the medioclavicular line) confirmed by ultrasound • Two abnormal (>upper limit of normal) serum liver enzyme levels (ALT, AST, gammaGT) • Ultrasound abnormalities other than hepatomegaly (increased heterogeneous echogenicity, nodularity, irregular margins) Current recommended practice is to offer an ultrasound test at annual review to determine a baseline value (from 5 years of age) and to monitor progression of

Item	Details
	disease thereafter. Clinical examination and biochemical liver tests may also be performed at this review and in interim periods as necessary. This review aims to assess the diagnostic accuracy of different diagnostic strategies to detect CF liver disease (including cirrhosis, portal hypertension and oesophageal varices) defined by gold standard tests and to identify whether any tests are useful in predicting the progression of CF liver disease.
Language	English
Population and directness	Infants, children, young people and adults with defined CF, diagnosed clinically and by sweat test or genetic testing. Population size and indirectness: • Studies with indirect populations will not be considered. • No restrictions to sample size.
Subgroups and sensitivity analyses	The following groups will be assessed separately if possible: • Children • Adults Sensitivity analysis: In the presence of heterogeneity sensitivity analysis will be conducted including and excluding studies with a high risk of bias. Important confounders: None identified
Index tests	• Clinical examination (hepatomegaly, splenomegaly) • Liver function blood tests (AST, ALT, GGT, Alkaline phosphatase, bilirubin, albumin, platelets and clotting) and indices based on these tests (eg APRI, Forn's score, INR ratio) • Imaging techniques – US • Liver stiffness measurement - transient elastography (Fibroscan) • Any of 1, 2, 3 or 4 alone or in combination
Reference standard	• Any of clinical examination, LFTs (AST, ALT, GGT) or ultrasound alone or in combination • Abdominal computed tomography (CT) • Magnetic resonance imaging (MRI) • Biopsy
Outcomes	For the diagnostic accuracy question: • Positive likelihood ratios/ Negative likelihood ratios (LR+/ LR-) • Sensitivity/ Specificity • Area under the curve (AUC) For the following target conditions: • Liver disease • Cirrhosis • Portal hypertension • Oesophageal varices For the prognostic question: • adjORs • adjHRs For the identification of: • Liver disease • Cirrhosis • Portal hypertension
Importance of outcomes	Critical outcomes for the diagnostic accuracy question: • Sensitivity/Specificity

Item	Details
	• Likelihood ratios Critical outcomes for the prognostic question: • Liver disease • Cirrhosis • Portal hypertension
Study design	• Test and treat studies • If test and treat studies not available we will aim to use both diagnostic accuracy and prognostic studies. For the diagnostic accuracy question: • Systematic reviews • Cross sectional diagnostic accuracy studies • Cohort studies (where cross-sectional data were reported therefore 2 x 2 table could be tabulated) • Case control studies will only be considered for inclusion where there is no evidence from cohort studies available For the prognostic question: • Systematic reviews • Prognostic cohort studies
Setting	Any healthcare setting where NHS care is delivered (primary, secondary, tertiary or community).
Search strategy	Sources to be searched: Medline, Medline In-Process, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase Limits (e.g. date, study design): Limit to English language only where possible (Medline and Embase). Apply standard exclusions filter. Supplementary search techniques: No supplementary search techniques will be used. See appendix E.14 for full strategies
Review strategy	Appraisal of methodological quality: • The methodological quality of each diagnostic study will be assessed using a quality checklists for diagnostic studies (QUADAS-2) as set out in the Developing NICE Guidelines Manual 2014. • For prognostic studies, the quality was assessed using the checklist created by Hayden et al. (2013) as set out in the Developing NICE Guidelines Manual 2014. • The quality of the evidence for an outcome (i.e. across studies) will be assessed using adapted GRADE approach. Synthesis of data: Meta-analysis will be conducted when appropriate. The cut-offs for diagnostic accuracy measures: • Sensitivity and specificity: ○ High >90% ○ Moderate 75-90% ○ Low <75% • Positive likelihood ratio: ○ Very useful test >10 ○ Moderately useful test 5-10 ○ Not a useful test <5 • Negative likelihood ratio: ○ Very useful test <0.1 ○ Moderately useful test 0.1 to 0.2

Item	Details
	○ Not a useful test >0.2 Imprecision of results: The sensitivity and specificity of each diagnostic test will be considered. The judgement of precision for sensitivity and specificity separately will be based on visual inspection of the confidence interval of the sensitivity value (decided that a CI with a width of <0.2 was deemed to be precise, ≥0.2 – 0.3 was downgraded to serious imprecision and ≥0.3 downgraded to very serious imprecision). • Review process: • A list of excluded studies will be provided following weeding. • Evidence tables and an evidence profile will be used to summarise the evidence.
Equalities	• Psychological and behavioural issues are more likely in people with a lower socioeconomic status. • Gender- outcomes are worse for women although there is no evidence that this is a consequence of difference in care. • Geographical issues – care is given through specialist centres and this may be a problem if a person with CF is living in an isolated location.
Notes/additional information	Not all people with CF will develop liver disease or progressively worsening liver disease. Therefore the Committee also queried the value of using ultrasound at annual review in addition to clinical examination and biochemical liver function tests when there was no indication of liver disease from these 2 tests in adults.