Table 74: Tests 1, 3, 4, 11, 19 & 20. Index tests (Clinical examination, biochemical testing and/or ultrasound) versus Biopsy CLFD definitions† to detect CFLD

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
Test 1. Clinical examination[a] to detect F1-F4 fibrosis in a population of children												

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	68 (95% CI: 61-77)*	33 (95% CI: 10-65)*	1.02 (95% CI: 0.67-2.23)*	0.97 (95% CI: 0.35-4.11)*	0.51 (95% CI: not reported)	HIGH
Test 4. ALT[b] to detect F1-F4 fibrosis in a population of children												
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[c]	30 (95% CI: 0-0.60)*	98 (95% CI: 96-100)*	1.34 (95% CI: 0-1408086.43)*	0.99 (95% CI: 0.94-1.04)*	0.59 (95% CI: not reported)	MODERATE
Test 3. Liver function tests[d] to detect moderate or severe fibrosis and cirrhosis and/or moderate to severe steatosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	83 (95% CI: 68-94)*	44 (95% CI: 26-58)*	1.49 (95% CI: 0.92-2.25)*	0.39 (95% CI: 0.11-1.22)*	not reported	MODERATE
Test 3. Liver function tests[d] to detect moderate or severe fibrosis and cirrhosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[c]	100 (95% CI: 78-100)*	44 (95% CI: 33-44)*	1.8 (95% CI: 1.17-1.8)*	0 (95% CI: 0-0.67)*	not reported	LOW
Test 11. Ultrasound[e] to detect F1-F4 fibrosis in a population of children												
1 (Lewindon 2011)	Cohort study	40	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	81 (95% CI: 73-89)*	44 (95% CI: 17-73)*	1.45 (95% CI:	0.44 (95% CI:	0.63 (95% CI: not	HIGH

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
			risk of bias						0.87-3.3)*	0.15-1.64)*	reported)	
Test 11. Ultrasound[f] to detect F1-F4 fibrosis in a population of children												
1 (Mueller Abt 2008)	Cohort study	30	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	65 (95% CI: 55-74)*	57 (95% CI: 22-87)*	1.52 (95% CI: 0.7-5.78)*	0.61 (95% CI: 0.29-2.06)*	not reported	HIGH
Test 11. Ultrasound[g] to detect moderate or severe fibrosis and cirrhosis and/or moderate to severe steatosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	70 (95% CI: 54-80)*	78 (95% CI: 58-92)*	3.13 (95% CI: 1.3-9.5)*	0.39 (95% CI: 0.22-0.8)*	not reported	MODERATE
Test 11. Ultrasound[g] t detect moderate or severe fibrosis and cirrhosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[c]	86 (95% CI: 61-97)*	70 (95% CI: 58-76)*	2.9 (95% CI: 1.45-4.13)*	0.2 (95% CI: 0.03-0.67)*	not reported	LOW
Test 19. Liver function tests[d] and ultrasound[f] to detect moderate or severe fibrosis and cirrhosis and/or moderate to severe steatosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	65 (95% CI: 50-76)*	78 (95% CI: 58-92)*	2.94 (95% CI:	0.45 (95% CI:	not reported	MODERATE

Number of studies (Reference)	Study design	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative Likelihood ratio (95% CI)	AUROC	Quality
									1.18-9.1)*	0.26-0.87)*		
Test 19. Liver function tests[d] and ultrasound[f] to detect moderate or severe fibrosis and cirrhosis in a population of children and adults												
1 (Lindblad 1999)	Cohort study	41	serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[c]	86 (95% CI: 62-97)*	74 (95% CI: 62-80)*	3.31 (95% CI: 1.6-4.9)*	0.19 (95% CI: 0.03-0.63)*	not reported	LOW
Test 20. Clinical examination[a], liver function tests[b] and ultrasound[e] to detect F1-F4 fibrosis in a population of children												
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	97 (95% CI: 85-100)*	13 (95% CI: 4-15)*	1.12 (95% CI: 0.89-1.18)*	0.22 (95% CI: 0-3.6)*	0.69 (95% CI: not reported)	HIGH
Test 20. Clinical examination[a], liver function tests[b] and ultrasound[e] to detect F2-F4 significant fibrosis in a population of children												
1 (Lewindon 2011)	Cohort study	40	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[c]	82 (95% CI: 62-95)*	48 (95% CI: 33-57)*	1.58 (95% CI: 0.93-2.22)*	0.37 (95% CI: 0.09-1.15)*	0.68 (95% CI: not reported)	MODERATE

Abbreviations: ALT: alanine transferase; AUROC: area under the ROC curve; CFLD: cystic fibrosis liver disease; CI: confidence interval
† Biopsy sampling was interpreted using Scheuer Scores in Lewindon 2011 and Mueller-Abt 2008. In Lindblad 1999 biospy samples were evaluated regarding fibrosis (normal; slight, enlarged portal zones; moderate, tendency towards septa formation; severe, bridging fibrosis; and cirrhosis, complete septa with regenerative noduli). Steatosis, bile duct proliferation, and inflammation were classified as absent, slight, moderate, or severe. A minimum of 4 portal zones were evaluated in each biopsy..
** Calculated by the NGA technical team from data available in the study report*
a. Clinical liver examination was to identify hepatomegaly with or without splenomegaly
b. Serum ALT levels were performed at enrolment. An abnormal result occurred at >1.5 upper limit of normal
c. 95% confidence interval for sensitivity was wide (width 20-30 percentage points)
d. Liver function tests included ALT, AST and GGT which had upper reference levels of 0.8, 0.8 and 0.5 µkata/ respectively.

e. Ultrasound liver images were recorded as nodular edge, nodular, heterogeneous, or normal echogenicity with or without splenomegaly. A normal ultrasound was defined as normal echogenicity with no splenomegaly. Ultrasound evidence of PHT included a nodular liver with splenomegaly.
f. Ultrasound images were categorised as normal, indeterminate (suggestion of liver disease but no definite signs of cirrhosis) and cirrhosis. Increased hepatic echogenicity, heterogeneity and/or increased attenuation in the absence of nodularity of the liver surface were classified as indeterminate. Splenomegaly as an isolated finding was also regarded as indeterminate. All patients with nodularity of the liver surface were classified as cirrhosis.
g. Ultrasonography was characterized as normal or pathological (increased and/or irregular echogenicity).