Table 73: Tests 5-7 & 17. Index tests (ALP, APRI, Forns score and Transient Elastography) versus practice guideline CFLD 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 5. ALP using laboratory determined age and gender specific cutoffs in a population of children and adults												
1 (Rath 2013)[a]	Cohort study	45	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	70.6 (95% CI: 49.5-85.5)*	82.1 (95% CI: 69.3-91.2)*	3.95 (95% CI: 1.61-9.74)*	0.36 (95% CI: 0.16-0.73)*	0.61 (95% CI: 0.44-0.79)	MODERATE
Test 6. APRI using a cut off of 0.133 in a population of children and adults												
1 (Rath 2013)[a]	Cohort study	45	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	47.1 (95% CI: 28.2-56.7)*	93.1 (95% CI: 82.0-98.7)*	6.82 (95% CI: 1.57-44.7)*	0.57 (95% CI: 0.44-0.88)*	0.75 (95% CI: 0.58-0.91)	HIGH
Test 6. APRI using a cut off of 0.231 in a population of adults												
1 (Karlas 2012)[c]	Cohort study	55	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	85.7 (95% CI: 60-97.4)*	70.7 (95% CI: 62.0-74.7)*	2.93 (95% CI: 1.58-3.86)*	0.20 (95% CI: 0.04-0.65)*	0.82 (95% CI: 0.69-0.91)	MODERATE
Test 6. APRI using a cut off of 0.4 in a population of adults												
1(Sadler 2015)[d]	Cohort study	122	serious[e]	no serious inconsistency	no serious indirectness	serious imprecision[b]	50 (95% CI: 29-69)*	92 (95% CI: 88-95)*	6.06 (95% CI:	0.55 (95% CI:	0.70 (95% CI:	LOW

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
									2.48-13.50)*	0.33-0.80)*	0.54-0.86)	
Test 6. APRI using a cut off of 0.5 in a population of adults												
1(Sadler 2015)[d]	Cohort study	122	serious[e]	no serious inconsistency	no serious indirectness	serious imprecision[b]	50 (95% CI: 29-68)*	94 (95% CI: 90-97)*	7.79 (95% CI: 2.99-19.44)*	0.53 (95% CI: 0.33-0.78)*	Not reported	LOW
Test 7. Forns score using a cut off of >2.154 in a population of adults												
1 (Karlas 2012)[c]	Cohort study	55	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	92.9 (95% CI: 67.8-99.6)*	61.0 (95% CI: 52.4-63.3)*	2.38 (95% CI: 1.43-2.71)*	0.12 (95% CI: 0.006-0.61)*	0.79 (95% CI: 0.65-0.89)	MODERATE
Test 17. Transient elastography using Fibroscan at a cut off of 3.7kPa in a population of adults												
1(Sadler 2015)[d]	Cohort study	127	serious[e]	no serious inconsistency	no serious indirectness	serious imprecision[b]	89 (95% CI: 66-98)*	37 (95% CI: 33-38)*	1.40 (95% CI: 0.98-1.59)*	0.30 (95% CI: 0.05-1.04)*	Not reported	LOW
Test 17. Transient elastography using Fibroscan at a cutoff of 5.3kPa in a population of adults												
1(Sadler 2015)[d]	Cohort study	127	serious[e]	no serious inconsistency	no serious indirectness	serious imprecision[b]	67 (95% CI: 43-85)*	83 (95% CI: 79-86)*	3.83 (95% CI:	0.40 (95% CI: 0.18-0.72)*	0.78 (95% CI: 0.65-0.92)	LOW

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
									2.04-5.87)*			
Test 17. Transient elastography using Fibroscan at a cutoff of 5.9kPa in a population of adults												
1 (Karlas 2012)[c]	Cohort study	49	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[b]	42.9 (95% CI: 22.6-49.6)*	97.1 (95% CI: 89.0-99.8)*	15.0 (95% CI: 2.06-328.3)*	0.59 (95% CI: 0.51-0.87)*	0.68 (95% CI: 0.53-0.80)	MODERATE
Test 17. Transient elastography using Fibroscan at a cutoff of 6.0kPa in a population of adults												
1(Sadler 2015)[d]	Cohort study	127	serious[e]	no serious inconsistency	no serious indirectness	serious imprecision[b]	56 (95% CI: 34-75)*	91 (95% CI: 87-94)*	6.06 (95% CI: 2.65-12.32)*	0.49 (95% CI: 0.27-0.76)*	Not reported	LOW
Test 17. Transient elastography using Fibroscan at a cutoff of 6.3kPa in a population of children and adults												
1 (Rath 2013)[a]	Cohort study	45	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	82.4 (95% CI: 64.2-85.3)*	98.2 (95% CI: 87.4-100)*	46.9 (95% CI: 5.1-25489647)*	0.18 (95% CI: 0.15-0.41)*	0.91 (95% CI: 0.78-1.00)	HIGH
Test 17. Transient elastography using Fibroscan at a cutoff of 6.8kPa in a population of adults												
1 (Kitson 2013)[f]	Case Control study	50	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	76 (95% CI: 61.6-82.5)*	92 (95% CI: 77.6-98.5)*	9.5 (95% CI:	0.26 (95% CI: 0.18-0.50)*	0.87 (95% CI: 0.77-0.98)	LOW

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
									2.75-55.6)*			

Abbreviations: ALP: Alkaline phosphatase; APRI: Aspartate aminotransferase to Platelets-Ratio-Index; AUROC: area under the ROC curve; CFLD: cystic fibrosis liver disease; CI: confidence interval; kPA: kilopascal

†Practice guideline definitions included criteria for clinical, biochemical and ultrasound testing.

** Calculated by the NGA technical team from data available in the study report*

a. Rath 2013 Diagnosis of CFLD (Flume 2007, Kerem 2005) if least 2 of the following conditions on at least 2 consecutive examinations spanning a 1-year period were present: (i) Hepatomegaly (liver span >2 cm below the costal margin on the medioclavicular line) confirmed by ultrasound, (ii) 2 abnormal serum liver enzyme levels (ALT, AST, γGT > ULN), (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins).

b. 95% confidence interval for sensitivity was wide (width 20-30 percentage points)

c. Karlas 2012 Diagnosis of CFLD (Sokol 1999, Colombo 2002) if at least 2 of the following conditions present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly;(2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT;(3) ultrasound abnormalities other than hepatomegaly (i.e., increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly).

d. Sadler 2015 Diagnosis of CFLD (Colombo 2002, Debray 2011) if least 2 of the following conditions were present: (i) Hepatomegaly and/or splenomegaly confirmed by ultrasonography, (ii) abnormal liver biochemistry consisting of elevated levels of any 2 of ALT, AST, or GGT, (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly presence).

e. High risk of bias being introduced from the patient flow

f. Kitson 2013 Diagnosis of CFLD (Colombo 2002, Debray 2011) if least 2 of the following conditions on consecutive examinations spanning a 1-year period were present:(i) Hepatomegaly and/or splenomegaly confirmed by ultrasound;(ii) abnormal serum liver enzyme levels, consisting of elevation above the upper limit of normal of 2 of the following: ALT, AST, GGT;(iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins; splenomegaly; presence of porto-systemic collateral veins; ascites).