LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

MRI-based technologies for the assessment of patients with non-alcoholic fatty liver disease [DAP59]

EAG Report: Supplementary material 2

Confidential until published

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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Caussy 2018[1]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Patients with suspected NAFLD indicated for a liver biopsy were recruited consecutively into a cross-sectional study.

Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study recruited patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed but it was unclear if these were patients who had indeterminate results from fibrosis testing, for whom TE or ARFI was unsuitable or who had discordant results from fibrosis testing.

Is there concern that the included patients do not match the review question?	**Concerns**	**UNCLEAR**

DOMAIN 2: INDEX TEST

A. Risk of Bias

The tests were performed by a radiologist blinded to the patient's clinical data. The thresholds of MRE were pre-defined.

Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Yes
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Liver biopsy performed by an experienced liver pathologist who was blinded to the patient's clinical and radiologic data.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Liver biopsy conducted 48 hours to one month after MRE.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Eddowes 2018[2]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Consecutive patients across two sites recruited to a cross-sectional study.		
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		No
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed and scheduled for non-targeted liver biopsy to stage fibrosis after inconclusive non-invasive assessment of fibrosis or to make a diagnosis after a range of non-invasive tests had not confirmed a diagnosis.		
Is there concern that the included patients do not match the review question?	**Concerns**	**LOW**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Index tests interpreted by a single operator blinded to the clinical findings and biopsy results. Unclear if the thresholds used were pre-specified.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Liver biopsy assessed by experienced academic liver histopathologists blinded to the MRI findings.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Two weeks interval between index test and reference standard.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Forsgren 2020[3]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Study recruited all patients who required a liver biopsy between 2007 and 2014.

Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study included patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed and patients with other liver disease aetiologies. Results were not presented separately for the population of interest to this assessment.

Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

No information provided on whether the results were interpreted without knowledge of the results of the reference standard. Thresholds were not pre-specified. Applicability concerns were judged to be high because the study used an investigational MRE design and not the Resoundant MRE platform that is commercially-available.

Were the index test results interpreted without knowledge of the results of the reference standard?		Unclear
If a threshold was used, was it pre-specified?		No
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**HIGH**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**HIGH**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

No information provided on whether the results of the liver biopsy were interpreted without knowledge of the results of the index test.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Index test and reference standard performed on the same day.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Hoffman 2020[4]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

The study recruited all patients with known or suspected hepatic fibrosis who underwent MRE between June and September 2018.

Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study included patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed and patients with other liver disease aetiologies. Results were not presented separately for the population of interest to this assessment.

Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Index test interpreted by two readers blinded to the histopathology or other clinical or laboratory findings.

Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		No
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

No information provided on whether the results of the liver biopsy were interpreted without knowledge of the results of the index test.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Three months between index test and reference standard. Not all patients received a reference standard.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		No
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**UNCLEAR**

Imajo 2021[5]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Patients who were being screened clinically on suspicion of NASH between January 2019 and February 2020.

Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study recruited patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed but it was unclear if these were patients who had indeterminate results from fibrosis testing, for whom TE or ARFI was unsuitable or who had discordant results from fibrosis testing.

Is there concern that the included patients do not match the review question?	**Concerns**	**UNCLEAR**

DOMAIN 2: INDEX TEST (LiverMultiScan)

A. Risk of Bias

Interpreted by image analysts who were blinded to the clinical data and risk grouping.

Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Yes
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 2: INDEX TEST (MRE)

A. Risk of Bias

No information provided on whether the MRE results were interpreted without knowledge of the results of the reference standard.

Were the index test results interpreted without knowledge of the results of the reference standard?		Unclear
If a threshold was used, was it pre-specified?		Yes
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

No information provided on whether the results of the liver biopsy were interpreted without knowledge of the results of the index test.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

All tests conducted at clinical visit 1.

Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Kim 2013[6]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Consecutive patients with NAFLD underwent MRE and/or liver biopsy.		
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study recruited patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed but it was unclear if these were patients who had indeterminate results from fibrosis testing, for whom TE or ARFI was unsuitable or who had discordant results from fibrosis testing.		
Is there concern that the included patients do not match the review question?	**Concerns**	**UNCLEAR**

DOMAIN 2: INDEX TEST

A. Risk of Bias

MRE performed prior to the reference standard. Thresholds were not pre-specified.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		No
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Liver biopsy results were examined by dedicated hepatopathologists who were unaware of the MRE results.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Liver biopsy performed within one year of the index test.		
Was there an appropriate interval between index test and reference standard?		No
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**UNCLEAR**

Kim 2020[7]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Patients with clinically suspected NASH who were scheduled to undergo or underwent liver biopsy within 2 months were identified from October 2016 to June 2017.

Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study recruited patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed but it was unclear if these were patients who had indeterminate results from fibrosis testing, for whom TE or ARFI was unsuitable or who had discordant results from fibrosis testing.

Is there concern that the included patients do not match the review question?	**Concerns**	**UNCLEAR**

DOMAIN 2: INDEX TEST

A. Risk of Bias

MRE performed prior to the reference standard. Thresholds were not pre-specified.

Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		No
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Reference standard interpreted by an experienced pathologist who was blinded to the patients' clinical and radiologic data.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Two months interval between index test and reference standard.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Pavlides 2017[8]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Patients with suspected or known NAFLD were invited to participate between May 2011 and March 2015.

Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study recruited patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed but it was unclear if these were patients who had indeterminate results from fibrosis testing, for whom TE or ARFI was unsuitable or who had discordant results from fibrosis testing.

Is there concern that the included patients do not match the review question?	**Concerns**	**UNCLEAR**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Analysis of index tests were performed by a blinded investigator. Unclear if the thresholds used were pre-specified.

Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Liver biopsies were evaluated by liver pathologists blinded to the MR data.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

One month interval between index test and reference standard.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Sofue 2020[9]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Consecutive patients recruited during a six-months period.		
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study included patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed and patients with other liver disease aetiologies. Results were not presented separately for the population of interest to this assessment.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Interpreted by a radiologist blinded to the patient clinical demographics and histopathologic findings. Thresholds were not pre-specified.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		No
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

No information provided on whether the results of the liver biopsy were interpreted without knowledge of the results of the index test.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Two months interval between index test and reference standard		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Toguchi 2017[10]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Consecutive patients with chronic liver disease recruited between October 2013 and January 2015.

Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study included patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed and patients with other liver disease aetiologies. Results were not presented separately for the population of interest to this assessment.

Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Results were interpreted by a radiologist who was blinded to the patient's clinical history. MRE was performed prior to the reference standard. Applicability concerns were judged to be high because the techniques for drawing regions of interest to calculate liver stiffness may not be representative of MRE in clinical practice.

Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		No
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**HIGH**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Results were interpreted by liver pathologists who were blinded to the patients' characteristics and results of the index test.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

The interval between index test and reference standard was less than 90 days.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Troelstra 2021[11]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Included the first 37 patients recruited to a separate study. Unclear how those patients were recruited.

Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study recruited patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed but it was unclear if these were patients who had indeterminate results from fibrosis testing, for whom TE or ARFI was unsuitable or who had discordant results from fibrosis testing.

Is there concern that the included patients do not match the review question?	**Concerns**	**UNCLEAR**

DOMAIN 2: INDEX TEST

A. Risk of Bias

The results were interpreted by a single observer blinded to the histopathology results. Applicability concerns were judged to be high because the study used an investigational MRE design and not the Resoundant MRE platform that is commercially-available.

Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		No
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**HIGH**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

The results were interpreted by a liver pathologist who was blinded to all other data.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Liver biopsy was performed within one week of the index test, with the exception of one participant whose biopsy was performed two months after the index test.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Trout 2018[12]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Patients who had undergone MRE between January 2012 and September 2016.		
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

The study included patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed and patients with other liver disease aetiologies. Results were not presented separately for the population of interest to this assessment.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Index test results were interpreted by a single observer who was blinded to the histologic data. Thresholds were not pre-specified.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		No
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Liver biopsy results were interpreted by a single pathologist who was blinded to the index test results.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

MRE and liver biopsy performed within three months of one another.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Xanthakos 2014[13]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

The study included 35 children and adolescents who were evaluated with MRE and liver biopsy as part of their clinical evaluation for chronic liver disease from August 2011 to December 2012.

Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

The study included patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed and patients with other liver disease aetiologies. Results were not presented separately for the population of interest to this assessment.

Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Interpreter of index test was blinded to the results of the reference standard. Thresholds were not pre-specified.

Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		No
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Interpreter of the liver biopsy results was blinded to the results of the index test.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Median of 1.5 months interval between index test and reference standard.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

2 NIH QUALITY ASSESSMENT OF CLINICAL IMPACT STUDIES

Table 1 NIH quality assessment of cross-sectional studies

Criteria	Caussy 2018[1]	Eddowes 2018[2]	Forsgren 2020[3]	Kim 2013[6]	Pavlides 2017[8]	Troelstra 2021[11]	Xanthakos 2014[13]
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	CD	CD	Yes	Yes	CD	CD	CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	Yes	No	No	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	No	No	No	No	No	No	No
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	No	No	No	No	No	No	No
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	NA	NA	NA	NA	NA	NA	NA

Criteria	Caussy 2018[1]	Eddowes 2018[2]	Forsgren 2020 [3]	Kim 2013[6]	Pavlides 2017[8]	Troelstra 2021[11]	Xanthakos 2014[13]
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	Yes	Yes	CD	Yes	Yes	Yes	Yes
13. Was loss to follow-up after baseline 20% or less?	NA	NA	NA	NA	NA	NA	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	No	No	No	No	No	No

CD=cannot determine; NA=not applicable

Table 2 NIH quality assessment of cohort studies

Criteria	Jayaswal 2020[14]	Gidener 2022[15]
1. Was the research question or objective in this paper clearly stated?	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	CD	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	Yes
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	Yes	No
13. Was loss to follow-up after baseline 20% or less?	Yes	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	Yes

CD=cannot determine; NA=not applicable

3 RISK OF BIAS ASSESSMENT OF RANDOMISED CONTROLLED TRIALS

Study details

Reference	Tonev 2020,[16] Perspectum Ltd 2021[17]

Study design

X Individually-randomised parallel-group trial
☐ Cluster-randomised parallel-group trial
☐ Individually randomised cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: LiverMultiScan Comparator: Standard of care

Specify which outcome is being assessed for risk of bias	Number of unnecessary liver biopsies
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Liver biopsies Proportion of patients in each arm for which liver biopsies could have been avoided

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial
X Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
X Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomisation process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Patients were be randomised using a 1:1 allocation, without blinding, to the LiverMultiScan (intervention) arm and the standard of care (control) arm. Randomisation was automatically calculated using a random number generator for patients who had been already stratified based on inclusion criteria and the recruitment site	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		N
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Patient characteristics were not reported for the two treatment arms, only for the whole study population	NI
Risk-of-bias judgement		High

N=no; NI=no information; Y=yes

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Open-label trial	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PY
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	The protocol reported that intention-to-treat analysis would be used but did not report any additional statistical analyses to estimate effect of assignment to the intervention. No details for the statistical analysis were provided in the CSR[17]	NI

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?		PN
Risk-of-bias judgement		Some concerns

CSR=clinical study report; N=no; NA=not applicable; NI=no information; PN=probably no; PY=probably yes; Y=yes

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Only 55/802 patients underwent liver biopsy	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Patients who were not suspected to have NASH/significant fibrosis would not be scheduled for liver biopsy. This means that authors could not confirm the true negative rate and false negative rate	Y
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		Y
Risk-of-bias judgement		High

N=no; NA=not applicable; NASH=non-alcoholic steatohepatitis; NI=no information; PN=probably no; PY=probably yes; Y=yes

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Histological score using the NAS CRN scoring system was appropriate to determine whether patient should have undergone liver biopsy	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	The liver biopsy procedure is standardised and should not differ between sites or patients	PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Open-label trial	PY
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Although it is possible that knowledge of the MRI data or SoC data could have influenced the NAS CRN score from liver biopsy, liver biopsy is a standard procedure which is done with prior knowledge in clinical practice	PY
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N

Risk-of-bias judgement		Some concerns

N=no; NA=not applicable; NAS CRN=NAFLD activity score; Clinical Research Network; NI=no information; PN=probably no; PY=probably yes; Y=yes

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	It is unclear whether a pre-specified analysis plan was finalised before data were available for analysis	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	All eligible reported results for the outcome domain correspond to all intended outcome measurements	N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low

N=no; Y=yes

Overall risk of bias

Risk-of-bias judgement		High

Summary of the risk of bias assessment of randomised controlled trials

Author	Outcome	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Tonev 2020,[16] Perspectum Ltd 2021[17]	Number of unnecessary liver biopsies	High	Some concerns	High	Some concerns	Low	High

4 CASP CHECKLIST ASSESSMENT OF THE QUALITATIVE STUDY

Table 3 CASP qualitative studies checklist

Item	McKay 2021[18]
Section A. Are the results valid?	
1. Was there a clear statement of the aims of the research	Yes
2. Is a qualitative methodology appropriate?	Yes
3. Was the research design appropriate to address the aims of the research?	Yes
4. Was the recruitment strategy appropriate to the aims of the research?	Yes
5. Was the data collected in a way that addressed the research issue?	Yes
6. Has the relationship between the researcher and the participant been adequately considered?	Yes
Section B. What are the results?	
7. Have ethical issues been taken into consideration?	Yes
8. Was the data analysis sufficiently rigorous?	Yes
9. Is there a clear statement of findings?	Yes
Section C. Will the results help locally?	
10. How valuable is the research?	
The authors discuss the implications of the study findings for clinical practice	

5 CHEERS CHECKLIST[19] SUMMARY OF THE INCLUDED STUDY IN THE COST EFFECTIVENESS REVIEW

Table 4 CHEERS checklist of economic evaluations

Section	Recommendation	Eddowes 2018[2]
Title and abstract		
Title	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Yes, page 631
Abstract	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Yes, page 631
Introduction		
Background and objectives	Provide an explicit statement of the broader context for the study	Yes, page 632
	Present the study question and its relevance for health policy or practice decisions.	Yes, page 631
Methods		
Target population and subgroup	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes, pages 632 and 634
Setting and location	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Yes, pages 632, 634
Study perspective	Describe the perspective of the study and relate this to the costs being evaluated.	Yes, page 634 (Decision analytic model)
Comparators	Describe the interventions or strategies being compared and state why they were chosen.	Yes, page 634 (Decision analytic model)
Time horizon	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Not reported but assumed to be short
Discount rate	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Not applied
Choice of health outcomes	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Yes, page 634 (Decision Analytic Model)
Measurement of effectiveness	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Not reported

Measurement and valuation of preference-based outcomes	If applicable, describe the population and methods used to elicit preferences for outcomes.	Not used
Estimating resources and costs	Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Total included including cost per diagnosis
Currency, price date, and conversion	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Currency is stated but price data and any conversion necessary not reported
Choice of model	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Yes, page 634
Assumptions	Describe all structural or other assumptions underpinning the decision-analytical model.	Yes, page 634
Analytical methods	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Yes, Supplement 1
Results		
Study parameters	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Yes, page 634 (Decision Analytic Model)
Incremental costs and outcomes	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Not reported
Characterising uncertainty	Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Not reported
Characterising heterogeneity	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information	Not reported
Discussion		
Study findings, limitations, generalisability, and current knowledge	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge	Not reported in terms of economic evaluation
Other		

Source of funding	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Yes, page 642
Conflicts of interest	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes, page 642

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