EAG report: ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

External Assessment Group report

ERRATUM

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Corrections to the Assessment Report

- Two factually inaccurate statments in the EAG report have been corrected (Section 5.3.3, p46 and Section 5.5, p65)
- The EAG also identified that the true negative and false positive data used to populate diagnostic test strategy T3 had inadvertently been transposed. The EAG has corrected this error and has reproduced all of the EAG report tables affected by this minor error (Table 12, Table 15 to Table 19)

5.3.3 Diagnostic test accuracy results

The absolute numbers of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) LiverMultiScan or MRE test results compared to the reference standard of liver biopsy (i.e., 2x2 data) were not presented in any of the included studies. We contacted the authors of all included studes to request these data.

Perspectum provided 2x2 data in response to the EAG request for information for the three LiverMultiScan studies[29,56,59] included in the DTA review. The authors of the Troelstra 2021[62] study of MRE provided 2x2 data in response to the EAG request. Data from the Kim 2020[58] study were obtained from a systematic review, and 2x2 data from the Kim 2013[57] study were calculated using the number of patients with and without the diagnosis of interest, and the estimates of sensitivity and specificity reported in the published paper. The full set of data sources is provided in Table 1.

Table 1 Data sources for 2x2 diagnostic test accuracy data

Study	Data source for 2x2 data	*Data provided for population in scope[23]
Eddowes 2018[29]	Perspectum Ltd submission[71]** included 2x2 data	Yes
Imajo 2021[56]	2x2 data were provided in the Perspectum Ltd submission.[71] However, inconsistencies in the data had to be resolved through personal communication with the study authors [Marika French, Perspectum, 3 February 2022]; data provided by the study authors were used in the EAG quantitative analysis. The EAG notes that the LiverMultiScan PDFF output, the LiverMultiScan cT1 output and the MRE test 2x2 data for diagnosis of steatosis and fibrosis provided by the Imajo 2021[56] study authors do not correspond to the numbers of patients with and without these diagnoses reported in Table 2 of the published paper;[56] the EAG was unable to clarify reasons for these discrepancies with the authors of the published paper.[56] The EAG also notes that data for advanced fibrosis (≥F3) were only available for LiverMultiScan tests and not for the MRE test	No
Kim 2013[57]	The EAG calculated 2x2 data using the number of patients with and without fibrosis (≥F3) and the estimates of sensitivity and specificity reported in the published paper	No
Kim 2020[58]	2x2 data were provided in Figure S7, S10 and S14 from the Selvaraj systematic review[72]	No
Pavlides 2017[59]	2x2 data (n=28) were provided in the Perspectum submission[71] and the EAG received IPD (n=48) from the study author [Michael Pavlides, University of Oxford, 9 December 2021]. The EAG used the summary 2x2 data for the quantitative analysis because the IPD used the Ishak staging system[73] to score fibrosis whereas the other included studies use the NASH CRN scoring system[17]	No
Troelstra 2021[62]	2x2 data were made available after personal communication with study authors [Marian Troelstra, Amsterdam University Medical Centers, 24 November 2022]	No

*In line with the final scope[23] issued by NICE, the population of interest consists of the three groups of patients with NAFLD for whom advanced fibrosis or cirrhosis has not yet been diagnosed, namely (i) patients with indeterminate results from fibrosis testing, (ii) patients who are unsuitable for testing with TE or ARFI and (iii) patients with discordant results from fibrosis testing.
** In this EAG report, references to the Perspectum submission[71] are to the evidence submission received by the EAG from Perspectum in response to the EAG request for information.
EAG=External Assessment Group; IPD=individual patient data

5.5 *Summary of EAG DTA and clinical impact review, and EAG quantitative analysis*

EAG DTA and clinical impact review

The EAG DTA review identified 13 studies[29,53-64] reported in 15 publications.[29,31,53-65] The EAG clinical impact review identified 11 studies[29,53,54,57,59,62,64,66-69] reported in 14 publications.[29,31,33,53,54,57,59,62,64-69] However, the EAG was only confident that one study (the Eddowes 2018[29] study) was carried out in the population described in the final scope[23] issued by NICE, namely patients with NAFLD for whom advanced fibrosis or cirrhosis had not been diagnosed:

- patients who have indeterminate results from fibrosis testing
- patients for whom TE or ARFI is unsuitable
- patients who have discordant results from fibrosis testing.

The clinical impact review only identified one RCT; the RADIcAL trial,[68] which was carried out by Perspectum Ltd. Results from this study[68] showed that, compared with patients in the standard care arm, [redacted] underwent unnecessary biopsies in the LiverMultiScan arm. Feedback from Perspectum Ltd[71] and the McKay study[69] was that patients and carers experiences of using LiverMultiScan were positive.

EAG quantitative analysis

The only relevant study[29] (n=50) identified by the DTA review focused on the potential of LiverMultiScan to deliver cost savings compared to biopsy and included clinical results (for example, cT1 and PDFF scores). The Eddowes study[29] categorised patients according to low- and high-risk of progressive liver disease. However, it was also possible to interpret the DTA data[71] generated by LiverMultiScan as follows: any fibrosis (≥F1), significant fibrosis (≥F2), Brunt Grade ≥1, Brunt Grade ≥2, NASH and advanced NASH. In response to a request from the EAG, Perspectum Ltd[71] also provided data for patients with advanced fibrosis (≥F3).

No DTA data were submitted to NICE by the manufacturer of MRE (Resoundant, Inc). Eleven studies[53-58,60-64] evaluated the DTA of MRE, but none of the studies explicitly included patients with indeterminate or discordant results from previous fibrosis testing.

The EAG carried out a quantitative analysis using data from six studies.[29,56-59,62] Where patients were diagnosed consistently across studies (fibrosis, steatosis, and NASH), the EAG carried out meta-analyses using cT1 and PDFF outputs for LiverMultiScan and for MRE.

Table 12 LiverMultiScan diagnostic test accuracy strategies and values (per 1,000 successful tests)

Diagnostic test strategy		cT1 cut-off value	Population prevalence	True positive	True negative	False positive	False negative	Sensitivity	Specificity
T1	Any fibrosis (≥F1)	800ms	87.0%	761	87	43	109	0.88	0.67
T2	Significant fibrosis (≥F2)	875ms	65.2%	413	261	87	239	0.63	0.75
T3	Advanced fibrosis (≥F3)	875ms	47.8%	304	326	196	174	0.64	0.63
T4	Brunt Grade ≥1	800ms	97.8%	782	0	22	196	0.8	0
T5	Brunt Grade ≥2	875ms	50.0%	348	348	152	152	0.7	0.7
T6	NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	875ms	54.4%	348	304	152	196	0.64	0.67
T7	Advanced NASH (NAS≥4 plus ≥F2)	875ms	47.8%	304	326	196	174	0.64	0.62
T8*	High risk (NASH or >F1)	875ms	79.4%	772	107	99	22	0.975	0.5

* Only sensitivity and specificity values were available from the Eddowes 2018[29] study the other values were calculated by the EAG
cT1= iron corrected longitudinal relaxation time; DTA=diagnostic test accuracy; F=fibrosis stage; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis
Source: Eddowes 2018 study/Perspectum Ltd[29,71]

Table 15 Initial LiverMultiScan outcomes generated by the EAG model (per 1,000 tests)

Diagnostic test strategy	cT1 cut-off value	True Positive	True Negative	False Positive	False Negative	Failed tests
T1: Any fibrosis (≥F1)	800ms	719.1	82.2	40.6	103.0	55.0
T2: Significant fibrosis (≥F2)	875ms	390.3	246.6	82.2	225.9	55.0
T3: Advanced fibrosis (≥F3)	875ms	287.6	308.2	184.9	164.3	55.0
T4: Brunt Grade ≥1	800ms	739.9	0.0	20.8	185.2	55.0
T5: Brunt Grade ≥2	875ms	328.9	328.9	143.6	143.6	55.0
T6: NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	875ms	328.9	287.3	143.6	185.2	55.0
T7: Advanced NASH (NAS≥4 plus ≥F2)	875ms	287.3	308.1	185.2	164.4	55.0
T8: High Risk (NASH or >F1)	875ms	729.5	101.1	93.6	20.8	55.0

cT1=iron corrected longitudinal relaxation time; EAG=External Assessment Group; F=stage of fibrosis; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis

Table 16 LiverMultiScan plus biopsy pathway: biopsies performed and averted (per 1,000 patients)

Diagnostic test strategy	cT1 cut-off value	Total number of biopsies, including those following a repeated LiverMultiScan at 6 months	Biopsies averted
T1: Any fibrosis (≥F1)	800ms	917.8	82.2
T2: Significant fibrosis (≥F2)	875ms	753.4	246.6
T3: Advanced fibrosis (≥F3)	875ms	691.8	308.2
T4: Brunt Grade ≥1	800ms	1000	0.0
T5: Brunt Grade ≥2	875ms	671.1	328.9
T6: NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	875ms	712.7	287.3
T7: Advanced NASH (NAS≥4 plus ≥F2)	875ms	691.9	308.1
T8: High Risk (NASH or >F1)	875ms	898.9	101.1

cT1=iron corrected longitudinal relaxation time; F=stage of fibrosis; MRI=magnetic resonance imaging; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis

Table 17 Pathway diagnostic test strategy costs (per 1,000 patients)

Diagnostic test strategy	cT1 cut-off value	LiverMultiScan plus biopsy pathway costs				Biopsy only pathway costs			Additional cost for the LMS pathway
		Biopsy procedures	Biopsy complications	LiverMultiScan test	Total costs	Biopsy procedures	Biopsy complications	Total costs	
T1: Any fibrosis (≥F1)	800ms	£738,817	£7,838	£411,556	£1,158,211	£805,000	£8,540	£813,540	£344,671
T2: Significant fibrosis (≥F2)	875ms	£606,451	£6,434	£511,311	£1,124,195	£805,000	£8,540	£813,540	£310,655
T3: Advanced fibrosis (≥F3)	875ms	£556,938	£5,908	£511,311	£1,074,157	£805,000	£8,540	£813,540	£260,617
T4: Brunt Grade ≥1	800ms	£805,000	£8,540	£411,556	£1,225,096	£805,000	£8,540	£813,540	£411,556
T5: Brunt Grade ≥2	875ms	£540,268	£5,732	£511,311	£1,057,310	£805,000	£8,540	£813,540	£243,770
T6: NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	875ms	£573,740	£6,087	£511,311	£1,091,137	£805,000	£8,540	£813,540	£277,597
T7: Advanced NASH (NAS≥4 plus ≥F2)	875ms	£557,004	£5,909	£511,311	£1,074,224	£805,000	£8,540	£813,540	£260,684
T8: High Risk (NASH or >F1)	875ms	£723,602	£7,676	£389,570	£1,120,849	£805,000	£8,540	£813,540	£307,309

cT1=iron corrected longitudinal relaxation time; F=stage of fibrosis; LMS=LiverMultiScan; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis

Table 18 QALY analyses for the two diagnostic pathways (per 1,000 patients)

Diagnostic test strategy	cT1 cut-off value	LiverMultiScan plus biopsy pathway					Biopsy only pathway				Incremental QALYs (LMS+biopsy pathway)*
		Biopsy procedure	Biopsy complications	Biopsy death	False negatives	Total QALY losses	Biopsy procedure	Biopsy complications	Biopsy death	Total QALY losses	
T1: Any fibrosis (≥F1)	800ms	5.12	0.13	1.29	1.55	8.10	5.58	0.15	1.41	7.14	-0.96
T2: Significant fibrosis (≥F2)	875ms	4.20	0.11	1.06	3.39	8.76	5.58	0.15	1.41	7.14	-1.63
T3: Advanced fibrosis (≥F3)	875ms	3.86	0.10	0.98	2.47	7.40	5.58	0.15	1.41	7.14	-0.27
T4: Brunt Grade ≥1	800ms	5.58	0.15	1.41	2.78	9.92	5.58	0.15	1.41	7.14	-2.78
T5: Brunt Grade ≥2	875ms	3.74	0.10	0.95	2.15	6.94	5.58	0.15	1.41	7.14	0.19
T6: NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	875ms	3.98	0.10	1.00	2.78	7.86	5.58	0.15	1.41	7.14	-0.73
T7: Advanced NASH (NAS≥4 plus ≥F2)	875ms	3.86	0.10	0.98	2.47	7.40	5.58	0.15	1.41	7.14	-0.27
T8: High risk (NASH or >F1)	875ms	5.02	0.13	1.27	0.31	6.73	5.58	0.15	1.41	7.14	0.41

* A negative value means that the biopsy only pathway generates more QALYs than LMS+biopsy pathway; a positive value means that the LiverMultiScan plus biopsy pathway generates more QALYs than biopsy only pathway

cT1=iron corrected longitudinal relaxation time; F=stage of fibrosis; LMS=LiverMultiScan; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year

Table 19 Incremental analyses for LiverMultiScan plus biopsy versus biopsy (1,000 patients)

Diagnostic test strategy	cT1 cut-off value	Incremental		ICER per QALY gained (versus biopsy)
		Costs	QALYs	
T1: Any fibrosis (≥F1)	800ms	£344,671	-0.96	LMS+biopsy dominated by biopsy
T2: Significant fibrosis (≥F2)	875ms	£310,655	-1.63	LMS+biopsy dominated by biopsy
T3: Advanced fibrosis (≥F3)	875ms	£260,617	-0.27	LMS+biopsy dominated by biopsy
T4: Brunt Grade ≥1	800ms	£411,556	-2.78	LMS+biopsy dominated by biopsy
T5: Brunt Grade ≥2	875ms	£243,770	0.19	£1,266,511
T6: NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	875ms	£277,597	-0.73	LMS+biopsy dominated by biopsy
T7: Advanced NASH (NAS≥4 plus ≥F2)	875ms	£260,684	-0.27	LMS+biopsy dominated by biopsy
T8: High risk (NASH or >F1)	875ms	£307,309	0.41	£749,886

cT1=iron corrected longitudinal relaxation time; F=stage of fibrosis; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year