MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
Perspectum	01	Whole document	1 onwards	There has been a continued focus on 'fibrosis' when Perspectum have made it clear from the beginning of the Diagnostic Assessment Programme and our HealthTech Connect registration, that we have delivered a service for distinguishing non-alcoholic steatohepatitis (NASH) from non-alcoholic fatty liver disease (NAFLD). We believe the focus of the diagnostics assessment report is categorically wrong and misleading as we have repeatedly presented evidence on why there is a gap in technologies to diagnose fatty liver disease. In our HealthTech Connect registration for NICE horizon scanning and several NICE meetings we have made it clear that the unmet need we are addressing is how to diagnose NASH non-invasively. NICE Guidance NG49 demonstrates that NICE recognise the unmet need for non-invasive accurate tests to diagnose NASH, and the safety and economic concerns regarding liver biopsy. We strongly agree with NICE's recommendation for non-invasive testing for diagnosing NASH and liver biopsy safety issues. As demonstrated from the evidence and comments submitted to NICE throughout this programme, Liver*MultiScan* responds to the NG49 recommendation and has the potential to reduce the number of unnecessary biopsies for patients at low risk of progression. Additionally, NG49 Section 1.1 'Diagnosing NAFLD in children and young people' does not include guidance on the diagnosis of NASH in children or young people. We believe this gap should be addressed to incorporate non-invasive accurate diagnostic tests. Without such guidance, there is a safety concern with the current gold standard for diagnosing NASH, liver biopsy; the incidence of liver biopsy complications (hospitalisation and major bleedings) has shown an increase with decreasing age (Thomaides-Brears et al., 2021).	In line with the final scope issued by NICE, the EAG considered all evidence that assessed diagnostic test accuracy of MRI-based technologies for fibrosis, inflammation and steatosis, including outcomes that considered more than one biomarker (e.g., a diagnosis of advanced NASH required that patients had NAS≥4 plus fibrosis ≥F2). NICE highlighted that the list of outcomes defined in the final scope[1] issued by NICE was non-exhaustive and that the EAG should consider all markers of NAFLD. The use of LiverMultiScan (LMS) to test for NASH (T6) and advanced NASH (T7) are strategies included in the EAG economic evaluation (EAG report, Section 6.2.2) for the population specified in the final scope[1] issued by NICE; the EAG has presented cost effectiveness results where only patients with high-risk NASH, defined by Perspectum Ltd as patients with cT1>875ms, are sent for biopsy. In an addendum to the EAG report, the EAG has provided an analysis where patients with a cT1<800ms do not have a second LMS at 6 months, in line with the pathway proposed by Perspectum Ltd. No diagnostic accuracy data are available linked to the use of LMS for children or young people.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				Furthermore, the importance of diagnosing NASH before advanced progression, including fibrosis, is recommended in documentation of some NHS Clinical Commissioning Groups (CCG) including East and North Hertfordshire CCG and City and Hackney CCG (East and North Hertfordshire NHS Trust, 2019, City and Hackney Clinical Commissioning Group). It was agreed that Liver*MultiScan* would not be considered as a comparator to pure markers of fibrosis see email 'Scope Query Date Confirmation and Stakeholder Input' (19th August 2021) prior to the scope workshop but this has been ignored.	
Perspectum	02	Whole document	1 onwards	Throughout the Diagnostic Assessment Report, advanced fibrosis (≥F3) data has been utilised beyond the intended use. It was stipulated that we are **not** positioning cT1 or PDFF as a diagnostic of advanced fibrosis (see email 'NICE assessment RADIcAL publication query' 15th March 2022). The data has been used in this context which is inappropriate. Perspectum provided clinical recommendations (DAR page 27) which highlighted three disease stages (fatty liver, NASH and high-risk NASH) which should have been considered over fibrosis levels.	The use of LMS to test for steatosis (T4 and T5), NASH (T6) and advanced NASH (T7) are strategies included in the EAG economic evaluation for the population specified in the final scope issued by NICE. In line with the final scope issued by NICE, the EAG considered all available evidence that assessed diagnostic test accuracy for fibrosis, inflammation and steatosis. NICE highlighted that the list of outcomes defined in the final scope was non-exhaustive and that the EAG should consider all markers of NAFLD.
Perspectum	03	17	2.1.2 Clinical impact (MRIbased technology: Liver*MultiScan)*	DAR: "*However, neither study reported results specifically for the subpopulation of patients with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed*." Please see comment 1 describing the continued focus on advanced fibrosis, and how being able to diagnose NASH non-invasively addresses the unmet need and research recommendations highlighted in NG49.	The EAG considered all available evidence that assessed diagnostic test accuracy of MRI-based technologies for fibrosis, inflammation and steatosis. NICE highlighted that the list of outcomes defined in the final scope was non-exhaustive and that the EAG should consider all markers of NAFLD.
Perspectum	04	18	2.1.2 Clinical impact	DAR: *"The test failure rate ranged from 0.0% to 7.6%."*	The EAG presented a narrative summary of test failure rate data from six studies identified by the EAG systematic literature review (SLR)

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
			(MRIbased technology: MRE)	The reported failure rate of MRE is underestimated and misrepresented. Please see the following articles which have been submitted with our comments that highlight the failure rate associated with MRE: 1. 'Magnetic resonance elastography in staging liver fibrosis in NAFLD: a pooled analysis of the diagnostic accuracy' 2. 'Technical Failure of MR Elastography Examinations of the Liver: Experience from a Large Single-Center Study' (3.5% at 1.5T and 15.3% at 3.0T) These papers also present the percentage of technical failures related to cirrhosis levels, BMI, aetiology, ascites, and iron levels	(Section 2.12). The failure rates reported are for patients with liver disease (all aetiologies) for whom advanced fibrosis or cirrhosis has not yet been diagnosed. A list of the reasons for excluding the studies on the reference lists supplied by the manufacturers is provided in the EAG report (Appendix 7). Magnetic resonance elastography in staging liver fibrosis in NAFLD: a pooled analysis of the diagnostic accuracy was excluded due to 'Wrong study design' (EAG report, p131), as it was a pooled analysis. Technical Failure of MR Elastography Examinations of the Liver: Experience from a Large Single-Center Study was not identified by the EAG searches as the search strategy was designed to focus on the index tests (i.e., LMS and MRE) and the target population (i.e., patients with NAFLD).
Perspectum	05	18	2.1.3 Cost effectiveness	DAR: *"Only one small LiverMultiScan study provided DTA and population prevalence data for patients described in the final scope issued by NICE."* Perspectum feel that the applied inclusion criteria is inappropriate. In each of the biopsy-paired Liver*MultiScan* studies shared (with the exclusion of pharma-sponsored clinical trials), the liver biopsy was performed as part of "standard care". Therefore, these are all relevant populations for this analysis – i.e., clinical biopsies performed as part of the	The relevant population is not *patients who had clinical biopsies performed as part of the current clinical pathway to manage patients with suspected NAFLD*. The relevant population is people with NAFLD for whom advanced fibrosis or cirrhosis has not yet been diagnosed: • who have indeterminate results from fibrosis testing • for whom transient elastography or ARFI is unsuitable to assess fibrosis

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				current clinical pathway to manage patients with suspected NAFLD. These studies reflect current clinical practice.	who have discordant results from fibrosis testing. The study protocol was designed to be in line with the final scope issued by NICE. The EAG applied the inclusion criteria set out in the study protocol. The EAG has presented test accuracy data for populations that are outside the final scope issued by NICE (only one study met the inclusion criteria). Alternative cT1 diagnostic test strategy data sources for sensitivity and specificity for diagnosing NASH (T6 and T7) using LMS are limited to results presented by Imajo 2021. The sensitivity and specificity results presented by Imajo 2021 are still below 100% and results from threshold analyses performed by the EAG show that even if accuracy was 100% LMS would not have an ICER per QALY gained for any strategy that was below £30,000. The use of alternative data sources would, therefore, not alter the conclusions that can be drawn from EAG model results. However, the EAG considers that generating cost effectiveness results using these data can lead to decisions being made based on data that are not relevant to the decision problem. Perspectum Ltd was sent a list of included studies by the EAG and was given the opportunity to suggest further studies that may have been missed by the EAG searches. Perspectum Ltd suggested the inclusion of additional studies; these studies were

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					assessed by the EAG and did not meet the EAG study inclusion criteria. A list of all excluded studies, with reasons for exclusion, is provided in the EAG report (Appendix 6 and Appendix 7).
Perspectum	06	19	2.1.3 Cost effectiveness	DAR: *"Using the available DTA and population prevalence data, EAG cost effectiveness results showed that LiverMultiScan is unlikely to be cost effective at current prices when used to triage patients with inconclusive results from previous fibrosis testing to biopsy."* *"The EAG was unable to generate cost effectiveness results for this technology; however, even if MRE was 100% accurate, due to high population prevalence estimates, it is unlikely that MRE would be cost effective at current prices."* Perspectum feels that the assessment method, and pathway being assessed is inappropriate and does not meet the intended use of Liver*MultiScan* presented to NICE from the HealthTech Connect horizon scanning and throughout the Diagnostic Assessment Programme. The following clinical recommendations have been presented by Perspectum (page 27) and have been ignored: 1. Consider reassessing patients with cT1 < 800ms (fatty liver) every 3 years (but NICE's economic model assumes 6 months) 2. Consider reassessing patients with cT1 800 to 875ms (NASH) after 6 months, but no mention of biopsy 3. Only consider biopsy for patients with a cT1 > 875ms (high risk NASH) if cirrhosis is suspected To biopsy all patients with a positive Liver*MultiScan* presents a direct conflict with Perspectum's clinical recommendations (comment 16) NG49 which recommends research to find a non-invasive test for diagnosing NASH. NG49 states that "*the only way to identify people with NASH is by performing an*	The EAG modelled diagnostic test strategies using the data made available by Perspectum Ltd. Clinical advice to the EAG was that patients in the NICE scope population who were suspected of having advanced fibrosis (F≥3), Brunt Grade ≥2, advanced NASH (NAS≥4 plus ≥F2) or high risk of progressive disease (NASH or >F1) after using non-invasive testing methods would be sent for a biopsy. The EAG notes that in both the Eddowes and Blake cost effectiveness analyses, all patients in the population of interest who were 'positive' (i.e., patients with high risk of progressive disease, including NASH) after LMS were sent for a biopsy. The EAG was not provided with any diagnostic accuracy data for patients who have a cT1 score between 800ms and 875ms. However, diagnostic accuracy data for patients with cT1 scores >875ms and <800ms were available and these data were included in the economic model (see EAG report). The EAG has generated a scenario in which patients with a cT1<800ms are not assessed at 6 months, patients with a cT1 800-875ms are assessed at 6 months and those with a cT1>875ms are sent for biopsy given that these patients were already scheduled for biopsy (see EAG Addendum).

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				invasive liver biopsy which is impractical in view of its risks to health and cost" however NICE is suggesting to biopsy everyone even if a non-invasive tool could be used to stratify patients. This stratification stops unnecessary biopsies and associated complications and costs. To biopsy all patients with a positive Liver*MultiScan* also contradicts several clinical guideline recommendations - BSG, EASL and AASLD (See attached evidence)- which agree that liver biopsy should be reserved only for patients at high risk of advanced liver disease or suspected concomitant secondary liver disease. In addition, documentation from East and North Hertfordshire NHS Trust highlights the safety, economic and clinical (inter-observer variation) issues with using liver biopsy to diagnose NASH, as well as patient reluctance.	The EAG considers that it is not appropriate to model <100% use of biopsy after a positive test result as data to inform assumptions are not available. An assumption of 100% use of biopsy after a positive test result is in line with the approach used in previous studies (Eddowes and Blake). Further, in the RADIcAL trial, whilst the reason (and number) of patients with a positive LMS test result who did not have a biopsy was unclear, a positive LMS test result could lead to a biopsy; the biopsy was considered necessary if a person was subsequently found to have NASH. The EAG reiterates that the data used in the EAG model relate to patients who were scheduled for a non-targeted liver biopsy.
Perspectum	07	19	3.2 Target condition	DAR: *"Approximately 7000 to 8000 patients per year undergo liver biopsy in the UK."* Of the 7000-8000 biopsies performed in the UK, additional information should be provided to better understand the following: 1. The proportion of patients that were suspected of having NAFLD and NASH, as opposed to liver disease not included in the scope. 2. The number of unnecessary biopsies conducted 3. How many biopsies were done in line with existing guidelines (National and CCG) This will help to demonstrate the number of biopsies being done to diagnose NAFLD and NASH in the UK.	The EAG is not aware of any published literature that provides this information.
Perspectum	8	20	3.2 Target condition	DAR: *"However, liver biopsy is an invasive procedure that is associated with well-recognised complications, including minor bleeding (1 in 500), severe intraperitoneal bleeding (1 in 2,500 to 1 in 10,000) and death (1 in 10,000 to 1 in 12,000)."*	The EAG has used UK data and explored the impact of biopsy complications on the magnitude of QALY loss in scenario/threshold analyses.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				Complication rates associated with biopsy can be found in the recent published systematic review and meta-analysis: 'Incidence of Complications from Percutaneous Biopsy in Chronic Liver Disease: A systematic Review and Meta-Analysis' (Thomaides-Brears et al., 2021) which has been submitted by Perspectum. Included complication rates include major complications (2.44%, with mortality at 0.01%, hospitalisation at 0.65%, major bleeding at 0.48% and moderate/severe pain at 0.34%) and minor complications (9.53%, pain 12.9%). Technical failure was high at 0.91%.	
Perspectum	9	20	3.2 Target condition	DAR: *"A NAS of ≥5 indicates a diagnosis of NASH."* An outdated NASH threshold has been presented here. A threshold of NAS ≥ 4 is more commonly used and NAS ≥ 4 and F ≥ 2 used as criteria for biopsy (EASL, 2021), and the typical enrolment criteria for NASH drug trials (Dennis et al., 2020). The threshold NAS ≥ 4 and F ≥ 2 has been used to determine the number of unnecessary biopsies conducted in a trial population and has been sent to NICE with these comments (New evidence mentioned in comment 31)	Thank you for the information about the threshold. It is not possible to update the EAG report at this stage of the DAR process.
Perspectum	10	20 & 21	3.2 Target condition	DAR: *"NASH - the build-up of fat in the liver leads to inflammation. Approximately 25% to 40% of patients with NASH develop liver fibrosis and approximately 20% to 30% of patients with NASH develop cirrhosis.[11] It is estimated that 3.3 million people in the UK have NASH,[6] and that approximately 80% of these people have undiagnosed NASH because early-stage NASH is usually asymptomatic.[12,13] It is widely accepted that liver fibrosis develops as a result of liver damage that is secondary to NASH.[14]"* *"Compared to patients with NAFLD with no fibrosis (F0), the risk of liver-related mortality in patients with NAFLD with fibrosis (F1 to F4) increases exponentially with each stage of fibrosis (F1, mortality rate ratio [MRR]=1.41, 95% CI 0.17 to 11.95; F2, MRR=9.57, 95% CI 1.67 to 54.93; F3, MRR=16.69,*	Thank you for this background information about the threshold. It is not possible to update the EAG report at this stage of the DAR process.

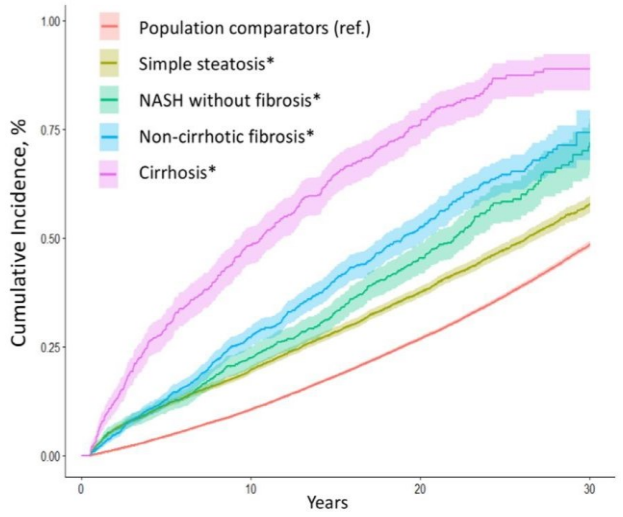
MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				95% CI 2.92 to 95.36; and F4, MRR=42.30, 95% CI 3.51 to 510.34).18 The risk of liver-related mortality in patients with NAFLD who have a fibrosis level ≥F2 is statistically significantly greater (p<0.02) than in patients with NAFLD who do not have fibrosis (F0).18" The increased risk of poor outcomes independent of fibrosis progression needs to be highlighted and include non-liver related outcomes (See below). Additionally, the risk of liver related mortality has been presented for NAFLD with fibrosis, not NASH. This needs to be updated to highlight the need for non-invasive tests to help assess those with NASH. The following papers have been sent with the comments: 1. 'Cancer Risk in Patients with Biopsy-Confirmed NAFLD: A Population-Based Cohort Study' 2. 'Mortality in Biopsy-Confirmed Nonalcoholic Fatty Liver Disease: Results from A Nationwide Cohort' 3. 'Clinical Outcomes in Biopsy-Proven Nonalcoholic Fatty Liver Disease Patients: A Multicenter Registry-Based Cohort Study'	

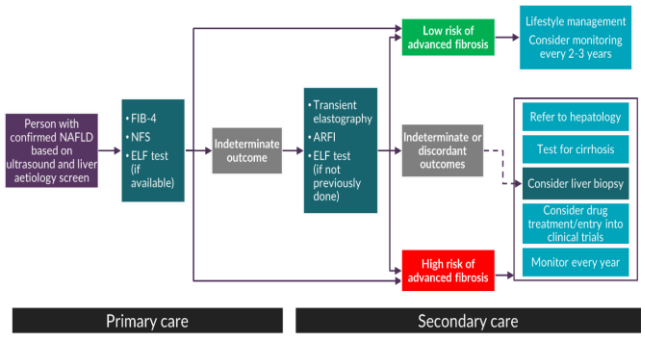
MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				 As argued by the Chief Medical Officer for England, there is a rising prevalence of comorbidities (Whitty et al. 2020). For NAFLD and NASH, there are several co-prevalent conditions, for example, in patients with a diagnosis of type 2 diabetes there is a 60% prevalence of NAFLD (Dai et al. 2017). In addition, meta-analysis of NAFLD in Korean populations revealed the incidence (per 1,000 person-years) of new-onset type 2 diabetes, hypertension, cardiovascular disease, and chronic kidney disease was found to be 16.9, 47.9, 100.6, and 13.9, respectively (Park et al. 2021). There is also evidence related to cardiovascular disease (CVD) prevention in the setting of diabetes and metabolic disorders (Cosentino et al., 2022).	

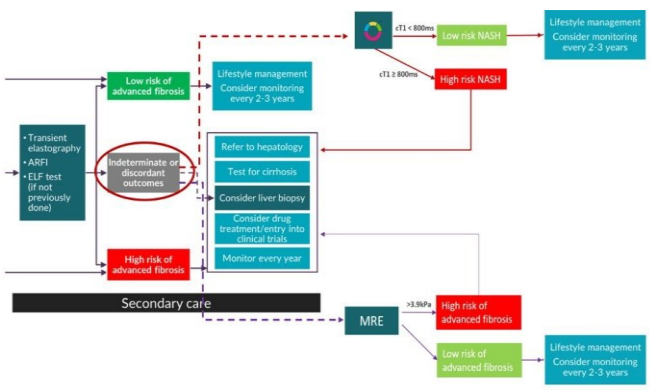
MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				The prevalence of comorbidities is supported in NG49; Recommendation 1.1.1. which states that NAFLD is more common in people who have type 2 diabetes or metabolic syndrome. Therefore, accurate staging of NAFLD is important to identify the most suitable care pathway and provides opportunity to slow or prevent disease progression to advanced stages including NASH and cirrhosis. Early diagnosis and management of liver disease is essential for improving outcomes (both liver and non-liver) and reducing the risk of complications in patients with NAFLD, especially when the disease is reversable.	
Perspectum	11	22	3.3 Current NHS diagnostic practice	DAR: The following pathway has been presented as an overview of current diagnostic pathway for the assessment of fibrosis in the NHS, based on guidelines and expert advice:  	The diagnostic pathway presented in the EAG report was extracted from the final scope issued by NICE. Prior to receipt of these comments, the EAG had not seen the alternative pathway presented by Perspectum Ltd. The EAG has generated a scenario in which patients with a cT1<800ms are not assessed at 6 months, patients with a cT1 800-875ms are assessed at 6 months and those with a cT1>875ms are sent for biopsy given that these patients were already scheduled for biopsy (see EAG Addendum). The EAG considers that it is not appropriate to model <100% use of biopsy after a positive test result as data to inform assumptions are not available. An assumption of 100% use of biopsy after a positive test result is in line with the approach used in previous studies (Eddowes and Blake). Further, in the RADIcAL trial, whilst the reason (and number) of patients with a positive LMS test result who

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				Perspectum notes the lack of inclusion of a NASH specific pathway and requests that this be included in the DAR. In addition, there is a conflict between those in the current pathway and the proposed pathway. Specifically, if a patient has a low risk of advanced fibrosis, they are given lifestyle management and monitored every 2-3 years. However, with the introduction of Liver*MultiScan,* the frequency of monitoring would increase from 2-3 years to every 6 months, even if a patient has a cT1 < 800ms (low risk). This is inconsistent and does not reflect proposed clinical implementation. A proposed pathway was sent to NICE (see below diagram), and despite being confirmed by NICE as correct, it has not been included in the DAR (See email 'LiverMultiScan: Pathway positioning and assessment' 27th October 2021) 	did not have a biopsy was unclear, a positive LMS test result could lead to a biopsy; the biopsy was considered necessary if a person was subsequently found to have NASH. The EAG reiterates that the data used in the EAG model relate to patients who were scheduled for a non-targeted liver biopsy.
Perspectum	12	23	3.3 Current NHS diagnostic practice	DAR: *"patients with NAFLD and an ELF score <10.51 are unlikely to have advanced liver fibrosis and should be reassessed regularly (adults every 3 years, and children and young people annually)"*	Thank you for this background information about the threshold. It is not possible to update the EAG report at this stage of the DAR process.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				Accuracy data for the ELF test in the target population have not been provided for this threshold. Perspectum requests that this be included, along with the supporting evidence, especially as this tool is recommended in published guidelines. Vali et al., 2020 and Younossi et al., 2021 have been provided.	
Perspectum	13	23	3.3 Current NHS diagnostic practice	DAR: *"The BSG national guidelines,[21] state that: a FIB-4 score <1.30 or a NFS <-1.455 demonstrates that patients have low risk of advanced fibrosis* • *patients with low risk of advanced fibrosis can be managed in primary care and advised on lifestyle modifications* • *patients with an indeterminate FIB-4 score (1.3 to 3.25) or NFS (-1.455 to 0.672) should undergo second-line testing using the ELF test, TE or ARFI* • *patients with FIB-4 score >3.25 or NFS >0.672 should be considered to have high risk of advanced fibrosis and should be referred to a specialist clinic irrespective of second-line tests* • *if the non-invasive tests are not able to exclude advanced fibrosis, then a liver biopsy should be considered to assess NAFLD and to rule out other concomitant liver diseases."* The BSG guidelines 'NAFLD – diagnosis, assessment and management' which outline recommendations for both NAFLD and NASH should be included in the DAR. This includes diagnosis of NASH and how to risk-stratify patients with NAFLD and NASH. It remains clear that there is a gap to diagnose NASH non-invasively and this is something that should be prioritised considering the current gold standard is liver biopsy (NG49). Liver*MultiScan* has been included in the risk assessment of liver fibrosis and inflammation in patients with suspected NAFLD in the following paper and can help with the above-	In Section 3.3 of the EAG report, the EAG has reported recommendations from the BSG national guidelines for the diagnosis of NAFLD and the non-invasive diagnosis of liver fibrosis. No recommendations for the diagnosis of NASH were presented in the BSG national guidelines.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				mentioned research recommendations: 'Multiparametric MR in patients with Non-alcoholic Fatty Liver Disease' (Schaapman et al., 2020)	
Perspectum	14	24	3.3 Current NHS diagnostic practice	DAR: *"Findings from a cross-sectional survey[25] of liver disease management, conducted from June to October 2020 indicated that only 25% (40/159) of UK Clinical Commissioning Groups (CCGs) used TE and only 16% (26/159) used the ELF test to assess liver fibrosis. Approximately two-fifths of UK CCGs (44%, 70/159) followed the BSG national guidelines[21] and used FIB-4 and NFS to assess liver fibrosis."* Perspectum would like to know how patients with NAFLD are being managed in CCGs that do not have access to any of these tests? This needs to be included, especially if it is being done using blood tests alone because this is not recommended by patient guidelines or by BSG NAFLD guidelines on the basis that a significant percentage of patients present without liver test abnormalities (BSG., 2021). These gaps in the availability of current tests demonstrates the urgent unmet need for non-invasive tests for assessing NAFLD and NASH across the UK. Published documents reveal that the ELF test has been reported as unavailable by Homerton University Hospital NHS Trust (East and North Hertfordshire NHS Trust, 2019) and that there is uncertainty in the availability of the ELF test (West Hertfordshire Hospitals NHS Trust, 2018). Furthermore, Jarvis and Hanratty (2016) report that the NICE recommendation for the use of ELF test in NAFLD poses challenges because it is unavailable in most NHS laboratories. Furthermore, East and North Hertfordshire CCG also state that ultrasound and liver function panels are not useful for stratifying the risk of NASH, steatosis and related conditions such as type 2 diabetes and chronic heart disease.	The EAG is not aware of any published literature that provides this information.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				We would propose that any subsequent guidance is not contingent on the above tests available, and provides guidance for clinicians in Trusts that do not have access to them.	
Perspectum	15	25	3.5 Population	DAR: *"In line with the final scope[23] issued by NICE, the population of interest is patients with NAFLD for whom advanced fibrosis or cirrhosis has not been diagnosed. This population consists of:* • *patients who have indeterminate results from fibrosis testing* • *patients for whom TE or ARFI is unsuitable* • *patients who have discordant results from fibrosis testing."* As mentioned in comment 14 above, there is a percentage of the population who are not being assessed with certain liver fibrosis tests (ELF, NFS and FIB-4). Therefore, Perspectum believes that the following sub-group should added to the patient population: • patients for whom fibrosis testing is not available	This population does not form part of the diagnostic pathway included in the final scope issued by NICE. Further, no diagnostic accuracy data are available for patients for whom results from fibrosis testing are not available.

Perspectum	16	28	3.6.1 Liver*MultiScan*	DAR: *Perspectum Ltd suggested to NICE[23] that the normal reference range for MRI PDFF is less than 5.6% liver fat content and that the diagnosis indicated by the cT1 output and the clinical recommendations are as follows:*
				• *<800ms: fatty liver*
				  ○ *no inflammation present*
				  ○ *reassess with MRI in 3 years*
				• *800 to 875ms: NASH*
				  ○ *recommend lifestyle modification manage type 2 diabetes and cardiovascular disease*
				  ○ *monitor disease status with MRI after 6 months*
				• *875ms: high risk NASH*
				  ○ *reassess with MRI every 6 months*
					Diagnostic accuracy data are not available to populate the additional analyses for patients with cT1 800-875ms scores.
					
					The EAG has generated a scenario in which patients with a cT1<800ms are not assessed at 6 months, patients with a cT1 800-875ms are assessed at 6 months and those with a cT1>875ms are sent for biopsy given that these patients were already scheduled for biopsy (see EAG Addendum).
					
					The EAG considers that it is not appropriate to model <100% use of biopsy after a positive

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				○ *consider liver biopsy if cirrhosis is suspected* ○ *cancer surveillance* ○ *consider inclusion in NASH therapeutic trials* The clinical recommendations provided by Perspectum have not been used to inform the economic model (See comment 6), and instead have been used to route patients to an invasive, hazardous, and costly procedure that contradicts the recommendations for non-invasive tests outlined in NG49. Additionally, the proposed model would place additional strain on the NHS and increase the MRI demand for NAFLD patients (Section 7.4.3) if patients with low-risk disease (< 800ms: fatty liver/TN) are scanned every 6 months as opposed to every 3 years.	test result as data to inform assumptions are not available. An assumption of 100% use of biopsy after a positive test result is in line with the approach used in previous studies (Eddowes and Blake). Further, in the RADIcAL trial, whilst the reason (and number) of patients with a positive LMS test result who did not have a biopsy was unclear, a positive LMS test result could lead to a biopsy; the biopsy was considered necessary if a person was subsequently found to have NASH. The EAG reiterates that the data used in the EAG model relate to patients who were scheduled for a non-targeted liver biopsy. The model assumption to re-scanning at 6 months was based on Perspectum advice for patients with cT1 scores of 800-875ms. The EAG considers that given the modelled population (i.e., those with a scheduled biopsy) it was appropriate to re-scan all patients at 6 months who had a cT1 score <875ms. The EAG has carried out a scenario in which all those with a cT1 score <800ms are not re-scanned at 6 months (see EAG Addendum).
Perspectum	17	28	3.6.1 Liver*MultiScan*	DAR: *"Perspectum Ltd does not propose that LiverMultiScan is suitable for staging fibrosis but considers that LiverMultiScan can stage NAFLD and distinguish between patients with NASH and High-risk NASH. However, in the EASL guidelines, liver biopsy is recommended as the reference standard for the diagnosis for patients with NAFLD".* As mentioned in comment 1, the intended use of Liver*MultiScan* has been misrepresented and it is categorically wrong and misleading. NICE Guidance NG49 demonstrates	In line with the final scope[1] issued by NICE, the EAG considered all available evidence that assessed diagnostic test accuracy of MRI-based technologies for fibrosis, inflammation and steatosis, including outcomes that considered more than one biomarker (e.g., diagnosis of NASH required that patients had NAS≥4 plus fibrosis ≥F2). NICE highlighted that the list of outcomes defined in the final scope issued by NICE was

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				that NICE recognise the unmet need for non-invasive accurate tests to diagnose NASH, and the safety and economic concerns regarding liver biopsy. We strongly agree with NICE's recommendation for non-invasive test for diagnosing NASH and liver biopsy safety issues. As demonstrated from the evidence and comments in the HealthTech Connect for horizon scanning and comments submitted to NICE throughout this programme, Liver*MultiScan* responds to the NG49 recommendation and has the potential to reduce the number of unnecessary biopsies for patients at low risk of progression.	non-exhaustive and that the EAG should consider all markers of NAFLD.
Perspectum	18	29	3.9 Reference standard	DAR: *"The reference standard is used to verify the presence or absence of fibrosis, inflammation and steatosis for patients with NAFLD."* Other markers of disease need to be mentioned throughout the report. Rather than focussing on fibrosis alone, other disease markers such as inflammation and steatosis should be highlighted, whilst describing the target condition.	The EAG has provided cost effectiveness results for a range of disease markers. The EAG highlights that, in the economic analysis, 5/8 diagnostic test strategies were not solely focused on fibrosis.
Perspectum	19	30	3.9.1 Liver biopsy	DAR: *"Clinical advice to the EAG is that, even after an MRI assessment, patients would be referred for biopsy if the following diagnoses were suspected:* • *advanced fibrosis (≥F3)* • *steatosis with Brunt grade ≥2* • *advanced NASH (NAS≥4 and ≥F3)* • *high risk of progressive disease (NASH or >F1)"* As highlighted in NG49, *"performing an invasive liver biopsy which is impractical in view of its risks to health and cost"* is the only way to identify people with NASH. Perspectum feel there is a need for better stratification of biopsy patients (See comment 6) and biopsies occurring in patients with suspicion of other types of cholestatic or autoimmune diseases. Having patients with the above diagnosis referred to biopsy will go against the objective of diagnosing patients non-invasively.	During the process of this appraisal the EAG took clinical advice from the EAG clinical advisor as well as the DAP Specialist Committee members who responded to EAG requests for information. The EAG has produced a model whereby non-invasive tests reduce the number of biopsies by identifying patients who may not have NASH, steatosis or fibrosis of differing severities. Patients most at risk of having these conditions (i.e., positive LMS test result) go on to have a biopsy. The company suggestion is that patients most at risk of having a specific condition (NASH) should not be biopsied. This is counter to the approach

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				This clinical advice is also inconsistent with our own experience of clinical guidance. We would recommend a wider pool of clinical experts are consulted.	adopted in the published studies (Eddowes and Blake) and the EAG model. The EAG highlights that in the RADIcAL trial, an unnecessary biopsy was defined as a 'biopsied patient who was diagnosed negative for NASH' (RADIcAL1 clinical report, p16).
Perspectum	20	30	3.9.1 Liver biopsy	DAR: *"Clinical advice to the EAG is that some patients (5% to 10%) do not wish to proceed with liver biopsy or are treated at centres without access to liver biopsy."* Perspectum feel that this value has been underestimated and the patient opinion of a costly invasive procedure should be accurately presented, especially if guidance such as NG49 is recommending research for a non-invasive alternative. Studies that we found that *"Although liver biopsy remains the gold standard to diagnose NASH, less than 25% of respondents routinely require it to make the diagnosis of NASH. We conclude that NASH underdiagnosed in gastroenterology and hepatology practices, highlighting the need to refine non-invasive diagnostic tools*" ('Practice patterns in NAFLD and NASH: real life differs from published guidelines'). Another paper highlighted the refusal rate of biopsy. *"It is worth noting that the median percentage of liver biopsy refusal is 75% in Romania"* ('Real-life Perception and Practice Patterns of NAFLD/NASH in Romania: Results of a Survey Completed by 102 Board-Certified Gastroenterologists').	In the EAG model, LMS is used as a 'biopsy triage tool' – the comparator is 'biopsy only'. Thus, the EAG model only includes the population for whom a biopsy is being considered. There is no diagnostic test accuracy data, or prevalence data for patients without a scheduled biopsy. Further, for this patient group, there is no evidence about how LMS test results affect a clinician 's decision to send a patient for a biopsy.
Perspectum	21	67	5.4.3 Intermediate outcomes, Patient acceptability of different testing modalities	DAR: *"However, clinical advice to the EAG is that the LiverMultiScan diagnostic report would not usually be made available to patients in NHS clinical practice."* The comment on whether the Liver*MultiScan* report is provided to patients in the NHS is very closed and cannot be assumed to represent the whole of the UK. It should be noted that	Advice from the EAG clinical advisor was included in the EAG report.

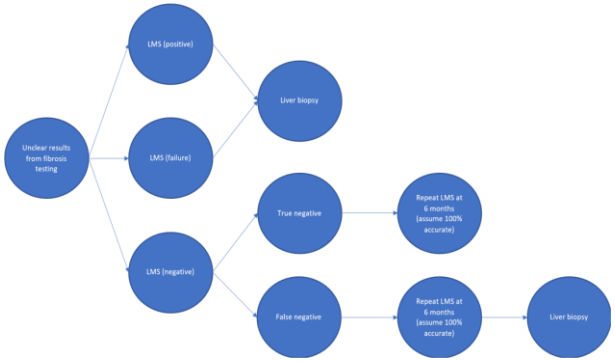
MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				Perspectum do not have advice against sharing the report with patients and it is up to the clinicians. As reported in the McKay et al. (2021) publication, patients find the report clear and understandable. In the USA, this report is typically shared with the patients as part of their clinical record. There is no technical nor regulatory reason why the report cannot be shared with the patient.	
Perspectum	22	69	5.5 Summary of EAG DTA and clinical impact review, and EAG quantitative analysis	DAR: *"The Eddowes study[29] categorised patients according to low- and high-risk of progressive liver disease; however, Perspectum Ltd[71] suggested six other ways of interpreting the DTA data generated by LiverMultiScan (from the same study): 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)."* The DAR states that *"Perspectum Ltd suggested six other ways of interpreting the DTA data generated by LiverMultiScan"* however this is incorrect. In the initial data request from Ms. Bresnahan (See attached email 'Data request on behalf of the Diagnostics Assessment Programme: 'MRI-based imaging for the assessment of non-alcoholic fatty liver disease' 23rd November 2021) Andrea Dennis (Perspectum) received a request for data from the Imajo et al. paper listing the following testing strategies and asking for the corresponding data. 1. Any fibrosis (≥F1) 2. Significant fibrosis (≥F2) 3. Advanced fibrosis (≥F3) 4. Brunt grade ≥1 5. Brunt grade ≥2 6. NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning) 7. Advanced NASH (NAS≥4 plus ≥F2) 8. High risk of progressive disease (NASH or >F1)	The EAG recognises Perspectum Ltd's position. The EAG report conforms to the final scope issued by NICE. The EAG has compiled an Erratum which includes the following text: "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)."

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				When providing study data for other publications, such as Eddowes et al., these same testing strategies were used to provide data so that the data can be compared easily. The full data request word document has also been provided (DataRequest_Imajo2021). As noted previously, Perspectum has never requested that Liver*MultiScan* is evaluated for the diagnosis of advanced fibrosis (≥F3).	
Perspectum	23	81	6.2.2 Model Structure	The following pathway has been presented in the DAR and was used to inform the model:  Perspectum have the following concerns regarding the model structure: 1. LMS positive/LMS negative/LMS failure rate: This contradicts the clinical recommendation thresholds that were provided by Perspectum (page 27) 2. LMS positive/LMS failure leading to liver biopsy. Again, this contradicts the clinical recommendations proposed by Perspectum and the NG49 research recommendations. It seems that even with a non-	The EAG was not provided with any diagnostic accuracy data for patients who have a cT1 score between 800ms and 875ms. However, diagnostic accuracy data for patients with cT1 scores >875ms and <800ms were available and these data were included in the economic model (see EAG report). The EAG has generated a scenario in which patients with a cT1<800ms are not assessed at 6 months, patients with a cT1 800-875ms are assessed at 6 months and those with a cT1>875ms are sent for biopsy given that these patients were already scheduled for biopsy (see EAG Addendum). 1. The EAG model is populated with data provided by Perspectum Ltd. 2. The EAG considers that it is not appropriate to model <100% use of biopsy after a positive test result as data to inform assumptions are not available. An

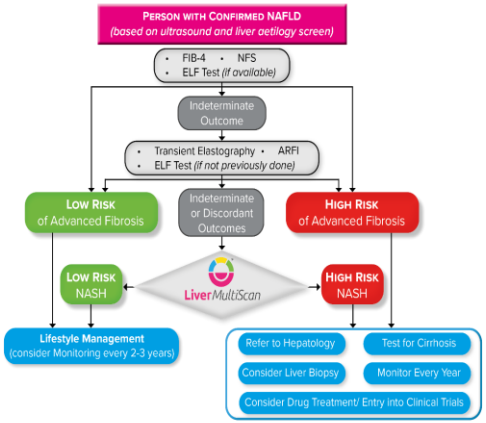
MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				invasive tool to help stratify patients, they will be sent for a costly, invasive procedure. This contradicts several clinical guideline recommendations - BSG, EASL and AASLD - which agree that liver biopsy should be reserved only for patients at high risk of advanced liver disease or suspected concomitant secondary liver disease. 3. True negative leading to repeat LMS in 6 months. This goes against not only the clinical recommendations provided by Perspectum, but the current NHS pathway (Figure 1). The reassessment frequency goes from 2-3 years to 6 months which seems like an unrealistic assumption and would put further strain on limited resources within the NHS. 4. False negative leading to a reassessment in 6 months. See point 3 above, and additionally, how would it be known if the test is a false negative? 5. Repeat LMS at 6 months leading to a liver biopsy. See point 1. As per the clinical recommendations, liver biopsy should only be considered for those with a cT1 > 875 (High risk NASH). Performing a biopsy on everyone with a positive Liver*MultiScan* would be unrealistic and unnecessary. Overall, it seems that even with a non-invasive tool that solves a research recommendation raised by NICE (NG49), an invasive procedure associated with safety and economic concerns will be performed, ignoring the clinical objective and duty or care to patients. The pathway below is an alternative that Perspectum believe should be modelled in this Diagnostic Assessment Programme, taking into account how current care (Figure 1) occurs:	assumption of 100% use of biopsy after a positive test result is in line with the approach used in previous studies (Eddowes and Blake). Further, in the RADIcAL trial, whilst the reason (and number) of patients with a positive LMS test result who did not have a biopsy was unclear, a positive LMS test result could lead to a biopsy; the biopsy was considered necessary if a person was subsequently found to have NASH. The EAG reiterates that the data used in the EAG model relate to patients who were scheduled for a non-targeted liver biopsy. 3. The EAG base case represents an optimistic scenario for Perspectum Ltd. Less frequent re-testing would increase QALY losses for patients with false negative results after the first LiverMultiScan. An EAG scenario has been provided in an addendum whereby patients with a cT1<800ms have do not have second LiverMultiScan at 6 months. 4. In the real world, it would not be known if the test result was a false negative result. The EAG assumption is that patients with false negative results are correctly identified at 6 months. The EAG base case analysis therefore represents an optimistic scenario for Perspectum Ltd. 5. This is the base case assumption used in the EAG model and justified above.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					Results from the EAG model show that introduction of non-invasive tests will reduce the number of unnecessary biopsies. The number of unnecessary biopsies that will be reduced depends on the definition of 'unnecessary'.
Perspectum	24	86	6.2.9 Biopsy complications	DAR: *"The Stevenson study[80] estimated the average costs (per biopsy) of treating complications"* We request that the EAG expand on the biopsy related complications and cost. What does this cost from the Stevenson study include? Typically, grade 3 or higher adverse events or complications would be included as these are expected to have an impact on costs. Given this, we are unclear on the rationale for these biopsy related complications. We recommend points for further investigation: 1. Most frequently occurring complications 2. Most severe complications 3. Cost of all complications	The EAG has implemented the adverse event (AE) frequencies and costs that were used in an economic model that formed part of a HTA of non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease. In that appraisal, the source of the frequency of complications was a systematic review of studies reporting AEs that were probably or possibly caused by the liver biopsy. The costing of AEs was based on assumptions – mortality was assumed not to incur a cost, and an AE was assumed to incur a hospital stay at a cost of £1,000.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
Perspectum	25	86-88	6.2.10 Utility values	DAR: *"The only utility values required in the EAG model are the disutilities associated with having a biopsy."* Provide more information on how the disutility value for failure to treat advanced liver disease was calculated/estimated. There is no further information in the reference (NG49). Currently, it is suggesting that patients expect biopsy related death to have a lower impact on quality of life compared to not being diagnosed with liver disease. Perspectum also request that a more recent reference be provided as this one is from 2012. If Implementing into the model, we suggest (as a minimum) making the QALY loss for a false negative either equal to the QALY loss for biopsy death.	The EAG has produced an addendum with the following statement that relates to this comment: "The EAG has assumed a disutility associated with a false negative LMS or MRE of 0.03 per annum. This is based on the difference in utility values for treated and untreated NASH in NG49. However, the actual value of a QALY loss associated with a false negative test result is uncertain. The possible sources of QALY loss associated with a false negative test result include: • symptomatic liver disease that develops after the false negative test result that would not have arisen following a true positive test result that led to treatment. This would include both liver disease that was present at the time of the false negative test result but was asymptomatic at that time, and symptomatic liver disease that developed after the false negative test result that may have been prevented with treatment • any loss in life years from a delay in diagnosis of advanced liver disease or progression of liver disease that could have been prevented with a correct diagnosis (which includes any survival benefit from the additional information that would have been generated through a biopsy after a true positive test result) On balance, as the QALY loss associated with a false negative only reflected treated versus untreated NASH, and not failure to diagnose

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					and treat more advanced liver disease, the EAG considers that the utility value used in the model is likely to underestimate the QALY loss from a false negative test result." The EAG was unable to identify alternative values to explore the impact of a false negative test result on QALY losses/utility values. The EAG undertook a scenario analysis in which the QALY loss was removed from the analysis (see EAG Addendum).
Perspectum	26	86-88	6.2.10 Utility values	DAR: *"The only utility values required in the EAG model are the disutilities associated with having a biopsy."* In the Stevenson et al (2012) paper, they state: *"For all patients who die as a result of biopsy, the costs of the biopsy are assumed to be incurred, but no further QALYs will be accrued. It is uncertain whether or not patients undergoing biopsy will suffer anxiety prior to the procedure; in order to address this issue and to assess the robustness of the results to this assumption, a sensitivity analysis was performed where the disutility associated with a biopsy was increased to 0.04 QALY (a value equivalent to approximately a fortnight with a utility of zero), which was deemed in consultations with clinicians to be an upper bound"* Perspectum would like to query why the value 0.04 QALY was not used in the analysis to represent the disutility associated with a biopsy.	The 0.04 QALY loss in Stevenson et al was arbitrary and based on a zero quality of life for 2 weeks. The 0.04 QALY loss was applied to all patients biopsied. The EAG does not consider that such a QALY loss is reasonable for all patients but has conducted a threshold analysis to highlight the size of the QALY loss from biopsy required to make LiverMultiScan or MRE cost effective at different willingness to pay thresholds per QALY.
Perspectum	27	86	6.2.8 Intervention and comparator costs	DAR: *"Unless otherwise stated, the intervention costs are presented in 2019/20 GBP* Perspectum would like to query the use of 2019/20 NHS cost tariffs. As per the National Payment Tariff System Report this was published on November 18th 2020.	The use of NHS Reference Costs is standard practice when carrying out NICE appraisals. The Reference Cost is based on an estimate using actual data from within the NHS of the cost of delivering specific activities to the NHS. At the time of the development of the

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					EAG model, these were the most up to date NHS Reference Costs available. The Tariff system is a construct to allow the internal market of the NHS to function and represents a transfer of income between different parts of the NHS. The Tariff is often based on the Reference Cost but is also frequently used to encourage/discourage different types of activity and so does not reflect the true cost of an activity to the NHS in the same way that Reference Costs do.
Perspectum	28	86	6.2.9 Biopsy complications	DAR: *"The Stevenson study[80] estimated the average costs (per biopsy) of treating complications associated with a percutaneous biopsy and a transjugular biopsy to be £7 and £13 respectively."* Rather than use the assumed cost of complication (£1000 from the Stevenson study), Perspectum would like to query why the following codes and associated costs were not utilised: • FD03A – Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+ • FD03B - Gastrointestinal Bleed with Multiple Interventions, with CC Score 0-4 • FD03C - Gastrointestinal Bleed with Single Intervention, with CC Score 8+ • FD03D - Gastrointestinal Bleed with Single Intervention, with CC Score 5-7 • FD03E - Gastrointestinal Bleed with Single Intervention, with CC Score 0-4 • FD03F - Gastrointestinal Bleed without Interventions, with CC Score 9+ • FD03G - Gastrointestinal Bleed without Interventions, with CC Score 5-8	The EAG has used the previously published value as the proportions of patients incurring the different complications are not known. To have any impact on the conclusions that can be drawn from EAG results for the most cost effective diagnostic test strategy (Brunt Grade 2), total biopsy complication costs would need to increase from £8.54 to £738.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				• FD03H - Gastrointestinal Bleed without Interventions, with CC Score 0-4 • FD05A - Abdominal Pain with Interventions • FD05B - Abdominal Pain without Interventions Perspectum feels that both major and minor complications should be accounted for in the model as they are associated with a real cost to the NHS. In addition, please provide the full breakdown off costs used in the model (What do tariff costs YG10Z and YG11A include?) e.g., whether staff, equipment, bed and monitoring costs are accounted for.	
Perspectum	29	96	6.2.14 Threshold analyses	DAR: *"In the dataset[29] used to populate the model, the diagnostic test strategy with the lowest population prevalence was advanced NASH (NAS≥4 plus ≥F2; 47.8%); however, for this diagnostic test strategy, the accuracy of the LiverMultiScan test was not close to 100% (sensitivity=0.64; specificity=0.62)."* Perspectum would like it to be known that the true accuracy of Liver*MultiScan* cT1 is much higher than that presented in the Eddowes paper. The strict (and inappropriate) inclusion criteria for the literature search have meant that superior accuracy data (Imajo, 2021) has not been included.	The study protocol was designed to be in line with the final scope issued by NICE. The EAG applied the inclusion criteria set out in the study protocol. The EAG has presented test accuracy data for populations that are outside the final scope issued by NICE (only one study met the inclusion criteria). Alternative cT1 diagnostic test strategy data sources for sensitivity and specificity for diagnosing NASH (T6 and T7) using LMS are limited to results presented by Imajo 2021. The sensitivity and specificity results presented by Imajo 2021 are still below 100% and results from threshold analyses performed by the EAG show that even if accuracy was 100% LMS would not have an ICER per QALY gained for any strategy that was below £30,000. The use of alternative data sources would, therefore, not alter the conclusions that can be drawn from EAG model results. However, the EAG considers that generating cost effectiveness results using these data

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					can lead to decisions being made based on data that are not relevant to the decision problem.
Perspectum	30	100	6.2.16 EAG analyses of uncertainty considered and rejected	DAR: "*If these patients were to receive a LiverMultiScan, cT1 and PDFF results would be available; however, this information is unlikely to influence treatment decisions and the reasons for not referring these patients for biopsy will remain despite access to LiverMultiScan results*." We would like it to be known that some specialist members of the Diagnostic Advisory Committee (DAC) are not users of Liver*MultiScan* and feel that this lack of experience will not provide an accurate representation of how clinical decisions can be influenced by the implementation of Liver*MultiScan*. In addition to the DAC, we would like to query the inclusion of clinician advice from experts not practicing in the UK, who are not specialist in the NASH space, rather autoimmune disease. There are instances of Liver*MultiScan* being used to influence treatment decisions such as informing treatment response to pharmaceuticals (Harrison et al., 2018 and Harrison et al., 2020). As mentioned in comment 32, we have new evidence that shows how clinical decision making can be influenced in Autoimmune Hepatitis patients using Liver*MultiScan* to detect sub-clinical disease and therefore feel that the following quotes might be unjustified: *"If these patients were to receive a LiverMultiScan, cT1 and PDFF results would be available; however, this information is unlikely to influence treatment decisions and the reasons for not referring these patients for biopsy will remain despite access to LiverMultiScan results."*	The EAG has no influence on the make-up of the DAC. The EAG requested specific information from the Specialist Advisory Committee when necessary. Further, the draft report was circulated to members of the Specialist Committee and the EAG's expert clinical advisor for comment.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				"…it is impossible to make an informed variations to the EAG model to accommodate a pathway in which patients who are identified as needing a biopsy (TP and FP) are not referred for a biopsy." *"Clinical advice to the EAG is that LiverMultiScan (or MRE) does not provide the level of detailed information that may be required to make treatment decisions, for example, clinical features that suggest cofactors for liver injury; this information is only available from a biopsy"* Throughout this assessment, we have provided evidence presenting how Liver*MultiScan* can be used to bridge the gap between current practice and the research recommendations highlighted in NG49 however it seems that invasive testing is being favoured regardless of the impact that is has on patients.	
Perspectum	31			**New evidence:** In the RADIcAL 1 trial, and specifically the biomarker cT1, correctly identified 9/10 of those patients biopsied that did not meet the criteria for a biopsy yet incurred an unnecessary biopsy following routine assessment using blood markers and ultrasound. Integrating multiparametric MRI for stratification prior to biopsy could avoid over 4000 liver biopsies annually in the UK and close to 100 major liver biopsy related complications. This evidence was sent to the NICE team on 1st April 2022 (See email 'NICE review of Liver*MultiScan* – why not focussing on avoidable biopsies') and is attached as additional evidence (See file RADIcAL 1-summary report_biopsy avoidance_v5_12Apr2022)	The new evidence provided by Perspectum Ltd relates to the use of LMS at a point in the diagnostic pathway that differs from the proposed positioning of LMS described in the final scope issued by NICE. Therefore, this evidence is not relevant to this appraisal. Further to the absence of 2x2 data, the EAG has some concerns about the RADIcAL trial methodology for determining LMS test accuracy. Concerns include: • only a small proportion of patients recruited to the trial supplied data • the rationale behind a patient having a biopsy was unclear • the results of previous testing was not provided and

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					• the time between the LMS and the biopsy was not reported.
Perspectum	32			**New evidence:** Liver*MultiScan* has demonstrated clinical utility in other liver disease (such as Autoimmune hepatitis (AIH)) and had a significant impact on clinical management and has the potential to inform patient risk stratification 'Quantitative magnetic resonance imaging to aid clinical decision making in autoimmune hepatitis'	The new evidence provided by Perspectum Ltd is not relevant to this appraisal. The final scope issued by NICE specified that the population to be appraised was "people with NAFLD for whom advanced fibrosis or cirrhosis has not yet been diagnosed: • who have indeterminate results from fibrosis testing • for whom transient elastography or ARFI is unsuitable to assess fibrosis • who have discordant results from fibrosis testing".
Perspectum	33			**New evidence:** Where the primary carer for a patient is not a hepatologist, and liver biopsy can be circumnavigated, Liver*MultiScan* has shown that it can be used to reliably identify liver disease – such as congenital heart disease patients with Fontan's circulation. '4D flow cardiovascular magnetic derived energetics in the Fontan circulation correlate with exercise capacity and CMR derived liver fibrosis'	The new evidence provided by Perspectum Ltd is not relevant to this appraisal. The final scope issued by NICE specified that the population to be appraised was "people with NAFLD for whom advanced fibrosis or cirrhosis has not yet been diagnosed: • who have indeterminate results from fibrosis testing • for whom transient elastography or ARFI is unsuitable to assess fibrosis • who have discordant results from fibrosis testing".
Perspectum	34			**Revised evidence:** 34_RADIcAL1_ClinicalReport_12Apr2022. The report has had the confidential tags removed so that it can be used and published in the Diagnostic Assessment Report	Thanks for the confidentiality update. The new evidence provided by Perspectum Ltd relates to the use of LMS at a point in the diagnostic pathway that differs from the proposed positioning of LMS described in the

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					final scope issued by NICE. Therefore, this evidence is not relevant to the EAG's economic analysis. Further to the absence of 2x2 data, the EAG has some concerns about the RADIcAL trial methodology for determining LMS test accuracy. Concerns include: • only a small proportion of patients recruited to the trial supplied data • the rationale behind a patient having a biopsy was unclear • the results of previous testing was not provided and the time between the LMS and the biopsy was not reported.
British Association for the Study of the Liver (BASL)	35	22	Figure 1	The current pathway (according to major guidelines and clinical practice) is that patients have a FIB-4 or NFS in primary care BEFORE they have a Fibroscan or an ELF. If indeterminate on FIB4, NFS then they have further testing. Therefore the second box on the right should only contain FIB4 and NFS.	The pathway was developed by NICE in consultation with expert advisors. It cannot be changed at this point in the process.
BASL	36	26	3.5.3	EASL guidelines state that patients with discordant results between Fibroscan and a patented serum test (NOT FIB4) should be considered for a biopsy.	Thank you for this background information. It is not possible to update the EAG report at this stage of the DAR process.
BASL	37	30	3.9.1	Patients would NOT be referred for a biopsy based on the isolated probability of steatosis with Brunt grade >=2. This is a very important misconception. Patients are only referred if there is suspicion of advanced fibrosis and/or advanced NASH. Some colleagues would also not refer for a biopsy if there was a high risk of progressive disease, defined as NASH or >F1.	In the EAG model, LMS is used as a 'biopsy triage tool' – the comparator is 'biopsy only'. The EAG model includes eight different diagnostic test strategies for consideration by NICE.
BASL	38	47	5.3.3	Liver Multiscan PDFF is NOT a marker of fibrosis and therefore there is no point for its diagnostic accuracy to be	PDFF analyses were included in the EAG report following a request from NICE (T1-T7).

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				reported for the evaluation of fibrosis. PDFF is an exclusive marker of steatosis.	
BASL	39	80	Table 12	The diagnostic accuracies presented are difficult to reconcile. The sensitivity of T2 is 0.63 and of T6 is 0.64, however the sensitivity of T12 (which in effect is T2 or T6) is 0.975.	The original EAG report included T8 data based on a cT1 algorithm that is no longer used. Perspectum Ltd re-analysed the high-risk data presented in the Eddowes publication using the new algorithm to bring the high-risk data (used to populate the T8 strategy) in line with the data for the other test strategies (T1 to T7). The new information has been included in the EAG Addendum.
BASL	40	77	Figure 10	It is not realistic to assume that when the Multiscan is repeated in patients who test negative, it will have 100% diagnostic accuracy (particularly when the specificity of the test is <0.7). This increases the effectiveness and potentially the cost effectiveness of the testing strategy in an unreasonable way.	The EAG accepts that this assumption is optimistic. If this assumption was modified, it would make LMS less cost effective. The EAG analyses of uncertainty is provided in the EAG report (Section 6.2.16)
Resoundant	41	39	5.3 Assessment of diagnostic test accuracy 5.3.1 Quality assessment Applicability concerns	"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." We would strongly encourage the authors to open the extensive literature to studies that include relevant populations that do not fit this narrow scope. Over the past 10-15 years, there has been significant inquiry into non-invasive alternatives to liver biopsy. Elastography techniques such as TE and MRE have been two of the more heavily investigated techniques to date, as elastography has shown significant promise as a surrogate for liver fibrosis. In these studies of TE and MRE, there has been much learned about confounders, applicability and accuracy in certain populations. By most accounts, TE works well when BMI is low and there is not significant fat and/or inflammation. However, there is still ongoing inquiry into the accuracy and applicability of TE and,	It is not possible to apply retrospective changes to the final scope issued by NICE. The EAG systematic review of clinical effectiveness evidence was inclusive: only one of the studies included in the review raised no concerns regarding the applicability of the study population (or the index test). In response to a request from NICE, the EAG generated cost effectiveness results using MRE 2x2 data presented by Imajo 2021 to populate diagnostic test strategies T1, T2, T6 and T7 (see EAG Addendum). The Imajo 2021 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

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				thus, consideration of how it can be deployed into a non-invasive clinical pathway. The NICE scope does not take this into account and seems to imply that for patients with an elevated TE, a biopsy is indicated and an additional MRI/MRE is not necessary. This fails to recognize that the number of false positives for TE is very high in NAFLD populations and this would subject many patients to unnecessary biopsy. Therefore, the narrowing of the literature base to only include studies where MRE was done as a result of an inconclusive TE exam ignores the fact that TE itself is still being actively investigated and that, given the large subpopulations with elevated BMI, that MRE might be the first-best-test for many patients. Further, the goal of advanced imaging (e.g., MRI) is to replace liver biopsy – not simply screen for patients for whom biopsy may not be indicated. Indeed, there is significant evidence that MRE predicts adverse liver outcomes and is suitable for determining patient care and monitoring, and MRE is used in the U.S. instead of biopsy to manage NAFLD/NASH patients (see AGA Guidelines, AASLD guidelines). **Authors should consider the suitability of MRE (and PDFF) to completely replace liver biopsy.** We strongly encourage NICE, in consideration of improving patient care and reducing liver biopsy dramatically, to re-examine the Scope and/or consider that a wider body of evidence can indeed satisfy the clinical workflow questions included within the Scope and how MRE and PDFF can be used to replace biopsy in the vast majority of cases.	was unsuitable or who had discordant results from fibrosis testing The EAG considers that it is not appropriate to model <100% use of biopsy after a positive test result as data to inform assumptions are not available. An assumption of 100% use of biopsy after a positive test result is in line with the approach used in previous studies (Eddowes and Blake). Further, in the RADIcAL trial, whilst the reason (and number) of patients with a positive LMS test result who did not have a biopsy was unclear, a positive LMS test result could lead to a biopsy; the biopsy was considered necessary if a person was subsequently found to have NASH. The EAG reiterates that the data used in the EAG model relate to patients who were scheduled for a non-targeted liver biopsy.
Resoundant	42	40 (and multiple others)	5.3 Assessment of diagnostic test accuracy 5.3.1 Quality assessment Applicability concerns	The study by Troelstra et al. needs to be removed. As stated earlier by Resoundant, this study employed an experimental, “homemade” MRE setup that is not approved for sale or clinical use anywhere in the world, including the UK. The inclusion of this study was flagged by Resoundant initially as inappropriate. Cut offs used in this study are not consistent with the world literature. For example, the cut off used or advanced fibrosis (≥F3) was 2.3 kPa – far below that reported in other studies (e.g., 3.6 kPa) and far below Resoundant’s	This study has not been removed. In line with the final scope issued by NICE, the EAG considered all available evidence that assessed the diagnostic test accuracy of MRI-based technologies for fibrosis, inflammation and steatosis. NICE did not specify that only data from the Resoundant, Inc. MRE platform that is commercially available should be considered.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				recommended cut off for F3. As such, the sensitivity was an unreasonably high 1.00.	
Resoundant	43	51	Individual study results: MRE	Regarding the Troelstra paper, authors note: "Clinical advice to the EAG was that the MRE G' shear modulus results were directly comparable with the MRE complex shear modulus results." This is incorrect, as G' alone is missing the G" component that makes up the complex shear modulus. To summarize: the shear modulus + loss modulus = complex shear modulus (G' + G" = G*). Only the complex shear modulus (G*) has been extensively validated for the clinical diagnosis of liver stiffness as a surrogate for liver fibrosis. Further, only the complex shear modulus is validated for clinical practice via the regulatory-approved versions of MRE. Comparing G' directly to G* ignores the G" component and changes the measurement and cut offs by a significant margin. As a matter of practice, the literature on MRE and the complex shear modulus (G*) is so extensive that there is no reason to expand the literature to include homemade, research versions of MR elastography that report different measurements. As in Comment 1 above, we simply encourage NICE to expand the included literature to include the majority of these papers studying DTA of MRE in the target populations.	It is not possible to apply retrospective changes to the final scope issued by NICE. The population included in the EAG systematic review was patients with NAFLD for whom advanced fibrosis or cirrhosis had not been diagnosed. However, only one of the studies included in the review raised no concerns regarding the applicability of the study population (or the index test). In response to a request from NICE, the EAG generated cost effectiveness results using MRE 2x2 data presented by Imajo 2021 to populate diagnostic test strategies T1, T2, T6 and T7 (see EAG Addendum). The Imajo 2021 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.
Resoundant	44	160	Table 22	The endpoints included seem arbitrary. For example, we do not know of any clinical scenario in which a diagnosis of steatosis (e.g., Brunt Stage 1 or 2 via imaging) would necessitate a liver biopsy. Of all of the components of NASH, only the onset and progression of fibrosis has been tied to adverse liver outcomes. Further, only fibrosis progression would qualify for patients for any pharmacologic treatments that may become available (similarly to Hepatitis C treatments, which required patients to be ≥F3 prior to approval for treatment). We would encourage the EAG to re-consider which endpoints are most important to clinical decision-making,	The EAG has presented a range of diagnostic test strategies for consideration by NICE. The strategies are based on information available from the literature and data provided by Perspectum Ltd.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				namely ≥F3 and cirrhosis. The endpoint of Advanced NASH (NAS>=4, >=F2) has been indicated by clinicians as clinically important – though most note that the fibrosis staging is far more important that the NAS components of the diagnosis. For this endpoint, combination approaches have shown promise, notably PDFF and MRE. We encourage the EAG to consider combination approaches involving MRE, such as 2D MRE and PDFF to assess advanced NASH, FIB-4+MRE, and the MAST score.	
Resoundant	45	General comment		The DAR and economic report should include the diagnosis of cirrhosis (F4) as an outcome of clinical importance, as this is a highly actionable endpoint.	The EAG model did not include this outcome as no relevant data were available.
Resoundant	46	General comment		PDFF is a generic biomarker which can be obtained on any clinical MRI scanner. It is not proprietary to Perspectum and should be evaluated as a generic, independent marker separate from any company's packaged offerings.	PDFF analyses were included in the EAG report following a request from NICE. Data from the relevant population were only available from Eddowes.
Resoundant	47	46	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 studies and the test manufacturers to request these data." Resoundant was not contacted by the EAG for 2x2 data for the studies which we submitted, or to assist with helping to acquire the 2x2 data. However, as stated previously, the 2x2 tables are not necessary if the sensitivity and specificity are reported, as 2x2 tables can be constructed from these important values using expected prevalence(s) that have been reported in other literature for NAFLD and NASH with fibrosis.	The EAG only contacted lead authors of included studies that did not report 2x2 data. Companies were not contacted directly for this information; however, one of the lead authors worked for Perspectum Ltd. The EAG has updated the EAG final report (and issued an erratum).
Resoundant	48	General comment		The addition of MRI to the diagnostic pathway should be aimed at replacing biopsy, not additive to ultrasound for ruling out invasive biopsy. MRE has shown high diagnostic accuracy for fibrosis and PDFF for NASH. Both are tied to long term outcomes and are acceptable for developing a care plan to hopefully avoid liver cirrhosis and/or decompensation.	It is not possible to make retrospective changes to the diagnostic pathway described in the final scope issued by NICE. The EAG considers that it is not appropriate to model <100% use of biopsy after a positive

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				Together, many countries are using these two noninvasive technologies to replace biopsy, rather than upstream from biopsy.	test result as data to inform assumptions are not available. An assumption of 100% use of biopsy after a positive test result is in line with the approach used in previous studies (Eddowes and Blake). Further, in the RADIcAL trial, whilst the reason (and number) of patients with a positive LMS test result who did not have a biopsy was unclear, a positive LMS test result could lead to a biopsy; the biopsy was considered necessary if a person was subsequently found to have NASH. The EAG reiterates that the data used in the EAG model relate to patients who were scheduled for a non-targeted liver biopsy.

Section B: Comments on the economic model (please add further rows as required)

Stakeholder	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
Perspectum	1	No comments are being provided on the economic model as Perspectum, believes that the proposed pathway and model structure needs to be changed. Please see comments 23 for issues with the current model and alternative pathway proposed.			The EAG has addressed Perspectum Ltd's comments on the EAG model - see EAG responses presented in Section A.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

		Written comments have been provided in the table above regarding the parameters chosen for the model and how these might be changed.			
Resoundant	2	Evaluation of MRE	Add an economic evaluation of MRE for a number of key endpoints that include fibrosis staging.	We completed a model for MRE (attached) and found that MRE would be highly cost-effective, saving the health care system -£75,989 per QALY gained for Advanced NASH (NAS>=4, >=F2). For other endpoints of interest, MRE would be similarly cost-effective: for example -£69,432 per QALY gained for the critical diagnosis of fibrosis ≥F3.	The cost and prevalence estimates used by Resoundant are not evidence based and the EAG therefore considers that Resoundant's results are unreliable. The EAG has produced cost effectiveness results using EAG preferred cost and prevalence data in the model used to generate the Resoundant MRE results (EAG Addendum). The EAG results suggest that MRE is less cost effective than the Resoundant results.
Resoundant	3	Prevalence	Add a literature-based expected prevalence for each endpoint of interest. For NAFLD, general prevalence has been shown to be 30-35% of the general population, with NASH with cirrhosis only expected to be <10% of this population. However, the proposed prevalence from the Eddowes study is not reflective of the NASH population, even after being screened by TE/ARFI.		The EAG estimated prevalence using data from a trial that considered the specific population described in the final scope issued by NICE. A range of prevalence threshold analyses have been carried out by the EAG (EAG Report and EAG Addendum).
Resoundant	4	Model a new code just for truncated MRE (and PDFF), as was done in the U.S.	In the NHS system, the cost for an MRE would be £148.24, the same cost as RD01A Scan of one area, without contrast, 19 years and over. However, MRE can be done in just four breath holds, and under 5 minutes – much shorter than the cost of RD01A. In the	We provided a model of a sample low cost MRE exam (£99) in our spreadsheet (attached) and found additional savings to the health system per QUAY gained (-£99,628).	In England, it is standard practice to use NHS Reference Costs to inform economic evaluations. The source of the cost of MRE to the NHS (£99) used in the analyses carried out by Resoundant is not known.

MRI-based technologies for the assessment of non-alcoholic fatty liver disease

Diagnostics Assessment Report (DAR) - Comments

			U.S., a new code for just MRE was created (CPT code 76391) at a reimbursement rate of ~$220 – lower than the cost of a typical abdominal MRI protocol. We would encourage the NHS and NICE to consider modeling a reduced cost code for MRE alone, as it is possible to implement a rapid, low-cost MRE exam in any Radiology practice setting.		The EAG has carried out threshold analyses to determine the cost at which MRE would become cost effective (EAG Addendum).
Resoundant	5	Model assumes PDFF only can be obtained via LiverMultiScan, which includes the additional cost of that company's analysis. However, PDFF is a generic biomarker that can be obtained on almost any MRI scanner, and reported by the Radiologist at no additional cost. Like MRE, PDFF is a rapid exam that can be done with a truncated protocol and thus cost less than a full abdominal MRI.	As with MRE, the analysis should explore a.) the cost of PDFF as simply that of an abdominal MRI scan (£148.24), or b.) as a truncated, low-cost protocol similar to MRE. It is possible to do MRE and PDFF together under this one low-cost protocol (e.g., £99).	The model should take into account a.) that PDFF can be done and reported at no additional analysis cost from Perspectum, and b.) that it can be done as part of a single, low-cost exam with MRE (e.g., £99).	No additional cost for undertaking a PDFF (LMS) has been included in the EAG analyses. The EAG has included cost effectiveness results relating to steatosis (T4 and T5). However, PDFF is an exclusive marker of steatosis and, in clinical practice, patients with steatosis are not routinely biopsied.