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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

MRI-based technologies for assessing non-alcoholic fatty liver disease

The following documents are made available to stakeholders:

1. **Stakeholder comments on the Diagnostics Consultation Document (DCD) and responses**

2. **Addendum to Diagnostics Assessment Report** - prepared by Liverpool Reviews & Implementation Group

2a. **Erratum to Addendum to Diagnostics Assessment Report** - prepared by Liverpool Reviews & Implementation Group

3. **Stakeholder comments on the Addendum**
   - Additional information submitted by Perspectum - FOI requests and waiting time summary

NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

MRI-based technologies for assessing non-alcoholic fatty liver disease
Diagnostics Consultation Document – Comments
Diagnostics Advisory Committee date: 28 September 2022

THEME: Impact of diagnosing NASH on clinical care and outcomes

Comment number	Name and organisation	Section number	Comment	NICE response
1	Perspectum Ltd	2.5	*"There are currently no treatments available specifically for NAFLD or NASH, but people with NASH or advanced fibrosis may enter clinical trials for new therapies."* This statement is factually incorrect. Many publications state that lifestyle interventions can be highly effective in treating NAFLD/NASH and is considered the main clinical recommendation and initial step for the management of NAFLD (Hallsworth et al., 2019, Ahmed et al., 2019, Michel and Schattenberg, 2020). NICE guideline NG7 (Preventing excess weight gain) states that clinicians should clearly communicate the benefits of maintaining a healthy weight, including the reduced risk of developing diseases associated with excess weight gain such as liver disease. The current EAG model does not consider a treatment option for those with NAFLD. As a comparison, a Health Technology Assessment by Crossan et al (2015) modelled the cost effectiveness of various index tests for diagnosing Alcoholic liver disease with the intervention being alcohol abstinence (which is equivalent to diet, i.e., food abstinence). **Why does NICE/EAG not consider lifestyle intervention as a treatment for NAFLD/NASH (as it does with abstinence in alcoholic liver disease) despite its well proven effectiveness? The model should be updated to incorporate this treatment option.**	Thank you for your comment, which the committee has considered. This wording has been updated in section 2.6 of the diagnostics guidance document to clarify: "There are currently no medicines available specifically for NAFLD or NASH…" The committee considered lifestyle interventions and the potential impact of the MRI tests on these at the first committee meeting (described in sections 3.2 and 3.5 of the diagnostics consultation document). A key uncertainty was what different lifestyle interventions would be offered if NASH was identified or how LiverMultiScan or MRE results affect people's adherence to lifestyle advice or interventions. Clinical experts highlighted that clinical management of NASH (if fibrosis is not detected) is generally the same as for simple fatty liver, and that there is currently no difference in extent of lifestyle-based interventions offered based on stage of liver disease (see section 3.2 of the diagnostics guidance document). No data were identified by the external assessment group (EAG) on the extent to which LiverMultiScan results change the use of lifestyle interventions in the NHS or people's adherence to these. Further research was recommended by the committee to address this uncertainty (see sections 3.21 and 4.1 in the diagnostics guidance document). The EAG commented that the same lifestyle advice would be provided for people with NAFLD irrespective of MRI results, and that there is no quantitative evidence to demonstrate that the uptake of lifestyle advice (and hence the effectiveness of this advice) is higher following a diagnosis

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				than prior to a diagnosis. It did threshold analysis on the size of the QALY gain that would be needed to be achieved through increased adherence to lifestyle interventions after MRI testing, and found, at thresholds of £20,000 and £30,000 per QALY gained, the QALY gain would need to be 0.013 and 0.009, respectively, for the Advanced NASH diagnostic test strategy (see EAG addendum 2, section 2.4). It also noted that negative MRI test results could disincentivize lifestyle changes (see section 3.5 of the diagnostics guidance document).
2	Perspectum Ltd	3.2	"*Clinical experts highlighted that clinical management of NASH (if fibrosis is not detected) is generally the same as for simple fatty liver."* **There should be mention of NG49 in this section for transparency. It should state that "*While* some *clinical experts highlighted that clinical management of NASH (if fibrosis is not detected) is generally the same as for simple fatty liver, this contradicts the clear recommendation for non-invasive tests to diagnose NASH (as of NG49)."** The diagnosis of NASH, even in the absence of advanced fibrosis, is important given both the increased risk of disease progression and adverse outcomes (Simon et al., 2021). Information regarding patient outcomes, how NAFLD can impact cancer risk and other adverse events was submitted during the DAR commenting period (no.10) however was ignored "*it is not possible to update the EAG at this stage of the DAR process"*. **What is the rationale for not permitting EAG updates during the review period of the DAR process? When are such updates permitted?**	Thank you for your comment, which the committee has considered. The research recommendation from NG49 on non-invasive tests for NASH was referenced in the diagnostics consultation document (section 2.4). Section 3.2 in the diagnostics guidance document has been updated to further reference this guideline and research recommendation for non-invasive tests for NASH. NG49 does not include recommendations on testing to identify NASH, as noted by a further comment submitted by this stakeholder (see comment 6 in this document: "…by the lack of NICE guideline recommendations on diagnosing and assessing NASH…"). Section 3.2 has been further updated to clarify this. The committee recognised that the risk of disease progression and adverse outcomes is increased with stage of NAFLD (see section 3.2 of the diagnostics consultation document and diagnostics guidance document). The final diagnostics assessment report (DAR) is circulated to registered stakeholders for comment. This is not a review period but rather commentary on the final report. The EAG are therefore not able to update the DAR once it has been

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				circulated to stakeholders. Any identified errors in the report can be corrected by an erratum. Stakeholder comments on the DAR are circulated to the Diagnostic Advisory Committee in advance of the first committee meeting for consideration in decision-making.
3 (part 1)	Perspectum Ltd	3.5	*"No data was available to determine whether LiverMultiScan or MRE affected people's understanding of NAFLD or their adherence to lifestyle advice or interventions."* **This statement is factually incorrect. Perspectum provided evidence (McKay et al., 2021) that was submitted to the EAG and dismissed despite containing relevant information on people's understanding of NAFLD or their adherence to lifestyle advice or interventions**. The McKay et al (2021) publication reviewed patient experience of Liver*MultiScan* and showing that it helped patients with chronic liver disease (including NAFLD) to understand their disease better than other modalities. This is another example of the EAG's flawed methodology of simply excluding data rather than questioning whether the NAFLD only components could be analysed or provided, as is best practice in systematic literature reviews. In contradiction, section 3.1 of the DCD states that "*The committee concluded that technologies that could reduce the need for liver biopsy would be likely to substantially benefit people and carers, in terms of health and impact on their lives"* however neglects to include that this can be inferred from the McKay paper. This was previously included in the response to the DAR but not properly addressed…	Thank you for your comment, which the committee has considered. The McKay et al. (2021) paper was included by the EAG in their review of clinical effectiveness and results were described in its report: "Most patients considered that the diagnostic report was very important for understanding their disease and helped them to feel empowered and involved in their clinical management" (see section 5.4.3 of the diagnostics assessment report). This paper was further discussed at the second committee meeting. Section 3.5 of the diagnostics guidance document has been updated to clarify the committee's considerations: "The committee acknowledged that McKay et al. (2021) provided evidence that LiverMultiScan improved some people's understanding of NAFLD. However, no data was available to determine whether LiverMultiScan or MRE affected people's adherence to lifestyle advice or interventions." Section 3.1 of the diagnostics consultation and diagnostics guidance documents contains reference to the testimonials reported in McKay et al. 2021 to support the conclusion that reducing liver biopsies would substantially benefit patients and carers.

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4	Perspectum Ltd	3.6	*"It further noted that the authors of the study report commented that the low number of people having liver biopsies was likely because there are no current treatment options for NASH."* It is understood that NICE cannot make recommendations about the future use of a technology, however Perspectum would like to note that it is highly likely that in the coming 1-2 years there will be an approved pharmacotherapy available for people with at-risk NASH. Given the high prevalence if NAFLD, it is fundamentally flawed to propose to assess them all by liver biopsy. Furthermore FIB-4 or TE are not suitable for longitudinal assessment or monitoring patient improvement or regression as they are less reliable in those between the ages of 35-65 years, have large indeterminate values requiring further evaluation, and biopsy may still be performed due to discordant clinical picture (Wentworth and Caldwell., 2021). Additionally, lifestyle intervention is an available and effective treatment option for NAFLD and NASH but has been omitted from the assessment as a viable treatment option, despite published literature (Hallsworth et al., 2019, Ahmed et al., 2019, Michel and Schattenberg, 2020) and the benefits of lifestyle intervention stated in NG7. Liver*MultiScan* cT1 has been used in multiple NASH clinical trials as a surrogate biomarker and is the only non-invasive tool to have reached the stage of having its "Qualification Plan approved" in the FDA's CDER Biomarker Qualification Programme. It should therefore be considered as a method to stratify patients for use of these likely expensive medicines in addition to monitoring efficacy. The earlier that clinicians are accustomed to using multiparametric MRI (LMS) in clinical practice, the smoother the roll-out of these pharmacotherapies will be.	Thank you for your comment, which the committee has considered. As noted, NICE diagnostics guidance takes into account current NHS care. The committee noted that new medicines for NASH are currently being developed and that if these became routinely available in the future this would likely increase the clinical impact of a NASH diagnosis (see section 3.2 of the diagnostics guidance document). Published guidance can be updated in the future if, for example, there is significant new evidence that is likely to change the recommendations or if there are changes to relevant care pathways (which could include new treatments becoming available). The process of reviewing and updating existing guidance is described in the CHTE programme manual on the NICE website. The committee considered lifestyle interventions and the potential impact of the MRI tests on these at the first committee meeting (described in sections 3.2 and 3.5 of the diagnostics consultation document). A key uncertainty was what different lifestyle interventions would be offered if NASH was identified or how LiverMultiScan or MRE result affect people's adherence to lifestyle advice or interventions. Clinical experts highlighted that clinical management of NASH (if fibrosis is not detected) is generally the same as for simple fatty liver, and that there is currently no difference in extent of lifestyle-based interventions offered based on stage of liver disease (see section 3.2 of the diagnostics guidance document). No data were identified by the external assessment group (EAG) on the extent to which LiverMultiScan results change the use of lifestyle interventions in the NHS or people's adherence to these.

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			Why does NICE/EAG not consider lifestyle intervention as a treatment for NAFLD/NASH given its well proven effectiveness?	Further research was recommended by the committee to address this uncertainty (see section 3.21 and 4.1 in the diagnostics guidance document). The EAG commented that the same lifestyle advice would be provided for people with NAFLD irrespective of MRI results, and that there is no quantitative evidence to demonstrate that the uptake of lifestyle advice (and hence the effectiveness of this advice) is higher following a diagnosis than prior to a diagnosis. It did threshold analysis on the size of the QALY gain that would be needed to be achieved through increased adherence to lifestyle interventions after MRI testing, and found, at thresholds of £20,000 and £30,000 per QALY gained, the QALY gain would need to be 0.013 and 0.009, respectively, for the Advanced NASH diagnostic test strategy (see EAG addendum 2, section 2.4). It also noted that negative MRI test results could disincentivize lifestyle changes (see section 3.5 of the diagnostics guidance document).
5	Perspectum Ltd	3.6	*"Therefore, unless the clinician suspects advanced fibrosis or cirrhosis, the clinical management will be the same for NAFLD or NASH."* Whilst Perspectum value some of the feedback and insights provided by the committee members, this comment was provided in the context of primary care management. Members of the committee who work in the secondary/tertiary care system commented that differentiation of NASH from NAFL is important to their management of patients. Differentiating NASH from NAFL is important as NASH is associated with increased risk of disease progression compared to patients with NAFL alone (Simon et al., 2021). Therefore, NASH patients require a more comprehensive assessment of stage and severity of disease to detect progression	Thank you for your comment, which the committee has considered. Specialist committee members (working in secondary or tertiary centres) highlighted in the committee meetings that clinical management of NASH (if fibrosis is not detected) is generally the same as for simple fatty liver, and that there is currently no difference in extent of lifestyle-based interventions offered based on stage of liver disease. They emphasised that the level of fibrosis or presence of cirrhosis are the main drivers of decisions about care. A clinical expert commented that if a specialist in secondary care identified a person with NASH but no fibrosis, they would discharge

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			to fibrosis/cirrhosis/HCC and to determine eligibility for NASH specific therapies in the near future (please see comment [2] and [3] for more information) Additionally, the committee acknowledged that the care of those with more advanced NAFLD may well be different from those with less advanced disease, for example, possible recommendation of bariatric surgery, diabetic management, or clinical trial enrolment. This was largely overlooked in the assessment and should be mentioned in the DCD. **There should be mention of NG49 in this section for transparency. It should state that "*Clinical experts from Primary Care highlighted that clinical management of NASH (if fibrosis is not detected) is generally the same as for simple fatty liver; however, clinical specialists highlighted that diagnosis of NASH is important, in agreement with the clear recommendation for non-invasive tests to diagnose NASH (as of NG49).*"**	them back to primary care (see section 3.2 of the diagnostics guidance document). The research recommendation from NG49 on non-invasive tests for NASH was referenced in the diagnostics consultation document (section 2.4). Section 3.2 in the diagnostics guidance document has been updated to further reference this guideline and research recommendation for non-invasive tests for NASH. NG49 does not include recommendations on testing to identify NASH, as noted by a further comment submitted by this stakeholder (see comment 6 in this document: "…by the lack of NICE guideline recommendations on diagnosing and assessing NASH…"). Section 3.2 has been further updated to clarify this.
6	Perspectum Ltd	3.17	*"Clinical experts said that there is a lack of clarity on how LiverMultiScan fits into the care pathway for NAFLD, and what care decisions the test result impact on."* For total transparency within the DCD regarding disease space, **Perspectum request that NICE state that there is no single consensus on the NAFLD/NASH care pathway in the UK and the types of tests used can vary on geographical area, hospital, and clinician**. This is highlighted by the lack of NICE guideline recommendations on diagnosing and assessing NASH and no recommendations for CCGs/ICSs without access to already included tests. The lack of a single pathway means, by default, there is no single place for Liver*MultiScan* in the care pathway.	Thank you for your comment, which the committee has considered. A statement has been added to section 2.2 of the diagnostics guidance document that specific tests and pathways used vary across the country. Section 3.21 of the diagnostics guidance document has also been updated to acknowledge that care pathways are variable: "Clinical experts said ~~that there is a lack of clarity on how LiverMultiScan fits into the care pathway for NAFLD~~ it is not clear what care decisions LiverMultiScan results would affect, or how people may adhere to lifestyle advice or interventions based on results".

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			Rather it would be used to diagnose NASH non-invasively as determined by the clinician. Therefore *"lack of clarity on how LiverMultiScan fits into the care pathway"* should not be used as a basis for not including Liver*MultiScan* into the care pathway. Published literature shows that a variety of tests are currently used to diagnose NAFLD and NASH, highlighting suboptimal screening for managing lifestyle interventions and comorbidities which are often not aligned with current guidelines (Ratziu et al., 2022, Rinella et al., 2022). It is important to note that in the AIM Specialty Health Clinical Appropriateness Guidelines (2022) Liver*MultiScan* has been deemed **medically necessary** for diagnosis and management of ANY of the following: 1. NAFLD in patients with high risk for cirrhosis due to advanced age, obesity, diabetes, or alanine aminotransferase (ALT) level more than twice the upper limit of normal 2. Other established chronic liver diseases when ultrasound elastography cannot be performed or is nondiagnostic. 3. Iron overload in hemochromatosis In addition, the American Association of Clinical Endocrinology (AACE) guidelines recommends Liver*MultiScan* cT1 as an appropriate referral strategy for those with indeterminate disease risk or high risk NAFLD (Cusi et al., 2022). Perspectum recommends that as a minimum, everyone who is indicated for a biopsy should have a Liver*MultiScan*, in addition to instances shown in both the AACE (Cusi et al., 2022) and AIM (2022) guidelines. This was previously included in the response to the DAR but not properly addressed.	

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7	Perspectum Ltd	3.17	*"The committee concluded that there is considerable uncertainty about how LiverMultiScan results would affect care in the NHS."* Uncertainty of NAFLD care in the NHS is not limited to Liver*MultiScan* but rather clinical practice as a whole: 1. There are variations in practice across the world as presented in published literature. (Rinella et al., 2022 and Ratziu et al., 2022). These publications highlight the differences in clinical care across fibrosis stages, and the percentage of surveyed physicians performing biopsies within clinical management. 2. There are geographical inequalities with existing tests which has not been considered in the model or recommendations (please see comment [19] for more information). 3. Currently lifestyle intervention and diet are used in the NHS as treatment for metabolic disease including NAFLD and NASH. This treatment option has been entirely overlooked (please see comment [1] for more information) **These points not only highlight the need for improved non-invasive testing, but should be included in the EAG cost-effectiveness modelling.**	Thank you for your comment, which the committee has considered. A key activity for the NICE diagnostics assessment programme is developing and publishing diagnostics guidance on selected diagnostic technologies for the NHS in England and its social care partners. Therefore, assessment is generally largely on clinical practice in England. A statement has been added to section 2.2 of the diagnostics guidance document that specific tests and pathways used vary across the country. See comment 19 for a response to point 2 in the stakeholder's comment. See comment 1 for a response to point 3 in the stakeholder's comment.

THEME: Need for confirmatory biopsy after positive MRI test

Comment number	Name and organisation	Section number	Comment	NICE response
8	Perspectum Ltd	3.16	*"The committee concluded that the MRI-based tests need further validation compared with biopsy."* Perspectum has submitted large cohort studies that show that Liver*MultiScan* cT1 can identify both at-risk NASH patients and	Thank you for your comment, which the committee has considered. The EAG's systematic review of clinical evidence used broad inclusion criteria (people with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed; diagnostics assessment report section 5.2). The

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those who have simple steatosis that can be managed in primary care. These thresholds have previously been submitted to NICE (Andersson et al., 2021) but was dismissed due to the study design. Perspectum feel that a meta-analysis validating the threshold for technology use are very relevant to the assessment of said technology.

The population being assessed in the DAP has resulted in multiple publications that validate LiverMultiScan's thresholds and use also being dismissed. Multi-centre validation studies with over 1500 unique biopsy paired datasets from over 10 clinical investigations have compared MR acquired data against histological criteria for disease (NASH clinical research network [CRN], grading and NAFLD activity score).
<table>
<tr><th>Publication</th><th>Disease</th><th>Biopsy paired</th><th>Unique biopsy paired</th></tr>
<tr><td>Banerjee, R., et al. (2014)</td><td>VH, NASH, ArLD, PSC/PBS</td><td>79</td><td>0</td></tr>
<tr><td>Eddowes, P., et al. (2017)</td><td>VH, NASH, ArLD, PSC/PBS</td><td>50</td><td>0</td></tr>
<tr><td>Pavlides, M., et al. (2017)</td><td>NAFLD</td><td>71</td><td>0</td></tr>
<tr><td>McDonald, N., et al. (2018)</td><td>VH, NASH, ArLD, PSC/PBS</td><td>142</td><td>142</td></tr>
<tr><td>Harrison, S.A. et al. (2019)</td><td>NAFLD</td><td>43</td><td>43</td></tr>
<tr><td>Levick C., et al. (2019)</td><td>NAFLD, VH, ArLD</td><td>19</td><td>0</td></tr>
<tr><td>Jayaswal et al. (2020)</td><td>NAFLD, VH, ArLD</td><td>178</td><td>178</td></tr>
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<td>
EAG has reviewed the publications highlighted in this comment and clarified why many of the studies were excluded (see EAG addendum 2 section 2.14). The EAG explained that evidence had been excluded because it reported populations that had been used in other studies (that were included in the EAG's report), or were not the focus of the assessment, or did not report validation against liver biopsy.

The committee discussed the need for further validation of LiverMultiScan against biopsy in the second committee meeting. It considered that the accuracy estimates used in the EAG's model from Eddowes et al. 2018 (which were specifically from people who had discordant results from previous fibrosis testing) were not particularly high (for example, for advanced NASH, 64% sensitivity and 62% specificity). These results were similar to those identified in the Imajo 2021 and Pavlides 2017 papers included in the EAG's clinical review (see diagnostics assessment report Figure 4). However, data from RADicAL1 provided by the stakeholder based on 18 people reported higher specificity (90%) for advanced NASH. The committee considered that further data on test accuracy would be highly beneficial to help estimate true test accuracy. However, the committee noted that validation against biopsy may underestimate test performance because of issues with sampling bias, and that there may also be issues with getting a biopsy result for a reference standard if this is not clinically indicated, or a person refuses biopsy. Therefore, the committee considered that studies which showed how well LiverMultiScan results predicted the occurrence of later clinical events could be used as an alternative to assess test performance. It noted the existing Jayaswal 2021 publication, but this study included multiple liver disease aetiologies (people with NAFLD, alcohol-related liver disease and viral hepatitis), and did not report results for NAFLD separately. For more
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<tr><td>Dennis et al. (2020)</td><td>NAFLD</td><td>86</td><td>0</td></tr>
<tr><td>Janowski et al., (2020)</td><td>AIH</td><td>60</td><td>0</td></tr>
<tr><td>Mole et al. (2020)</td><td>Cancer</td><td>128</td><td>128</td></tr>
<tr><td>Amerikanou et al., (2021)</td><td>NAFLD</td><td>98</td><td>98</td></tr>
<tr><td>Dennis et al. (2021)</td><td>NAFLD</td><td>264</td><td>0</td></tr>
<tr><td>Imajo et al., (2021)</td><td>NAFLD</td><td>145</td><td>0</td></tr>
<tr><td>Harrison et al., (2021)</td><td>NAFLD</td><td>260</td><td>260</td></tr>
<tr><td>Beyer et al., (2021)</td><td>NAFLD</td><td>581</td><td>581</td></tr>
<tr><td>Janowski et al., (2021)</td><td>AIH/ASC</td><td>66</td><td>66</td></tr>
<tr><td>Andersson et al., (2021)</td><td>NAFLD</td><td>543</td><td>26</td></tr>
<tr><td>Total</td><td></td><td>2270</td><td>1522</td></tr>
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How does the committee justify the statement that there is insufficient biopsy paired data given the above table with more than 1500 unique biopsy paired patient data points? If the committee still has concerns around patient population, why haven't they asked us for a breakdown or sub-analysis of the data as is often done in meta-analyses, or asked the EAG to widen the patient population being assessed?
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<td>information, see sections 3.19 and 4.1 of the diagnostics guidance document.</td>
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<td>9</td>
<td>Perspectum Ltd</td>
<td>3.11</td>
<td>"A patient expert commented that if confirmatory biopsy was needed after a positive MRI test result (see section 3.10), introducing MRI could also increase the time to diagnosis compared with a pathway in which liver biopsy is done without a preceding MRI test."</td>
<td>Thank you for your comment, which the committee has considered.

The EAG provided a scenario analysis in which no confirmatory biopsy was done after a positive MRI test result (see EAG addendum 2, section 3.3), which the committee discussed at the second committee meeting on the 28th</td>
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			Perspectum agree with this statement and would like to reiterate that a positive Liver*MultiScan* is sufficient to inform patient management. Liver*MultiScan* is not intended to lengthen the NAFLD diagnosis pathway and increase wait times for patients. Liver*MultiScan* is intended to diagnose these patients quicker, and non-invasively. Currently unpublished results from RADIcAL-1 show that including Liver*MultiScan* in care pathways led to fewer tests (and associated hospital visits) being performed, a quicker time to diagnosis and an increased certainty in diagnosis. This was previously included in the response to the DAR but not properly addressed.	September (see section 3.10 of the diagnostics guidance document). Clinical experts commented that current data on test performance was not sufficient to be confident in a diagnosis without a biopsy. The committee concluded that if further data provides reassurance on test performance, a follow-up biopsy may not always be needed, but that it is inappropriate to assume that the tests can replace biopsy entirely. The committee noted that RADIcAL1 was the only study identified by the EAG that showed the impact of LiverMultiScan on biopsy use (see section 3.6 of the diagnostics guidance document), which showed about a 30% decrease in biopsy use. This was similar to the impact of LiverMultiScan on biopsy use in the EAG's base case, but much lower than the scenario analysis provided for the second committee meeting (which modelled a 100% decrease in biopsies following LiverMultiScan use). At the committee meeting on the 28th September, a company representative for Perspectum stated that the LiverMultiScan would not entirely replace biopsy but could help identify people who could most benefit from it. The EAG explained that their base case model assessed the use of LiverMultiScan to identify people who did not need biopsy.
10	Resoundant		We appreciate the EAG's work on this important topic. Our general thoughts are that the original Scope could be improved by focusing on MRI-based technologies that can replace liver biopsy – not simply help rule-in/rule-out liver biopsy. We would encourage the EAG to consider re-opening the Scope in the near future to better take advantage of novel non-invasive technologies such as MRE, which are being used in many healthcare systems to non-invasively stage liver fibrosis and guide patient care, without the need for liver biopsy.	Thank you for your comment, which the committee has considered. The EAG provided a scenario analysis in which no confirmatory biopsy was done after a positive MRI test result (see EAG addendum 2, section 3.3), which the committee discussed at the second committee meeting on the 28th September (see section 3.10 of the diagnostics guidance document). Clinical experts commented that current data on test performance was not sufficient to be confident in a diagnosis without a biopsy. There was no test accuracy data for MRE

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				in the scope population. Additionally, no data was identified assessing MRE using the thresholds given for advanced fibrosis or cirrhosis. The committee concluded that data on MRE performance is needed in populations that match the scope, either from subgroup analysis of existing studies, or further accuracy studies, and that more data on the test accuracy of MRE is needed using prespecified thresholds set by the company, done in a population not used to derive these thresholds (external validation) (see sections 3.16 and 3.20 of the diagnostics guidance document). If further data provides reassurance on test performance, a follow-up biopsy may not always be needed, but that it is inappropriate to assume that the tests can replace biopsy entirely (see sections 3.10 and 3.16 of the diagnostics guidance document).

THEME: Impact of liver biopsy

Comment number	Name and organisation	Section number	Comment	NICE response
11	Perspectum Ltd	2.4	*"However, liver biopsy is an invasive procedure that is associated with well-recognised complications including bleeding and death".* While this statement is correct (although complications rates are higher than commonly reported (Thomaides-Brears et al., 2021)), **Perspectum would like NICE to acknowledge that liver biopsies are also regularly refused in NHS practice, highlighting the need for a non-invasive alternative for patients not willing to undergo an invasive biopsy.** Since 2017, South Warwickshire NHS Foundation Trust has had an average liver biopsy refusal rate of 4.94% (South Warwickshire NHS Foundation Trust, (2022), provided under the Freedom of Information Act 2000) showing that patients are at risk of being unmanaged if they decide not to opt for an invasive, risky test. Anecdotal information from UK clinicians estimates that this	Thank you for your comment, which the committee has considered. The EAG modelled a scenario in which no biopsy was done in either the intervention or comparator arms to examine potential for cost-effectiveness for people who do not want biopsy, and estimated the number of additional QALYs LiverMultiScan would need to generate to achieve an ICER of £30,000 per QALY (see EAG addendum 2, section 3.2). The committee noted that it was still unclear for this population what changes to care would be made based on the MRI test results, and therefore how the additional QALYs

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			refusal rate can be as high as 50% in NAFLD/NASH care pathways (we would be happy to introduce you to these clinicians for further discussion). In addition, it is clear from patient testimonials (McKay et al., 2021) that biopsy is a painful and invasive procedure that patients would rather avoid: • "*Biopsy was very stressful and very painful. (The MRI) was a walk in the park in comparison to that"* • *"It felt exactly like you had been stabbed, which basically I suppose you have been"* • *"Because it was non-invasive. It doesn't cause me any problems. It's quick, it doesn't affect anything. Whereas with the alternative, a liver biopsy would be completely the opposite"* • *"I had two biopsies. I had one in 2011 and one in 2014. It's excruciatingly painful… And then you go back home, and this pain comes there for a number of days to heal up. Then that alone itself – the second time felt like I was going to have a panic attack… The drama that goes with a liver biopsy. They are separating you like an operation – it's traumatic. You know they make you feel as if they are going to chop you up. I wouldn't want to go through any liver biopsy again."*	could be generated (see section 3.11 of the diagnostics guidance document). Section 3.1 of the diagnostics guidance document contains reference to the testimonials reported in McKay et al. 2021 to support the conclusion that reducing liver biopsies would substantially benefit patients and carers. The committee recognised that reducing the need for liver biopsy would be likely to substantially benefit people and carers in terms of health and impact on their lives, and considered this in its decision-making.
12	Perspectum Ltd		*"However, liver biopsy is an invasive procedure that is associated with well-recognised complications including bleeding and death".* While this statement is correct, it is not clear how the disutility associated with liver biopsy death has been calculated within the EAG model. It appears to assume that each individual that dies as a consequence of liver biopsy loses 1 QALY. This suggests that	Thank you for your comment, which the committee has considered. The EAG provided an explanation of how this disutility was calculated in the diagnostics assessment report (section 6.2.10) and repeated this in its second addendum (section 2.3).

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			the QALYs lost in subsequent years (year 2, 3, 4 etc) has been ignored. **Perspectum requests that in-depth calculations are provided by the EAG to allow a more thorough review, and these disutility values are re-estimated.**	
13	Perspectum Ltd	3.1	*"The committee also noted that the risk of complications from liver biopsy is higher for people with very high BMI, who are at higher risk of having nonalcoholic fatty liver disease."* Whilst Perspectum agrees with this comment, the cost of treating biopsy complications (£8.54) has been grossly underestimated within the EAG's model. The value (£8.54) is based on the Stevenson et al. (2012) HTA where the authors hypothesise a hospital stay is "*assumed to cost £1000"*. This original assumption is not evidence based and is unfeasibly low for a hospitalisation cost associated with a serious adverse event and does not match the utility vignette of *"equivalent to approximately 10 weeks with a utility of zero or a year with a utility decrement of 0.2".* **Why did the EAG not update this assumption on cost of hospital stay given it is one of the primary mechanisms of value for the technology under question (averting adverse events and associated costs)?** **Additionally, as it is recognised that there is a risk of mortality associated with biopsy and a disutility value within the model, why is there not cost associated with a biopsy death?**	Thank you for your comment, which the committee has considered. At the first committee meeting, the EAG explained that the £8.54 cost was an average over all people included in the model, and that the cost of each individual complication was higher (£1,005 in the base case, see EAG addendum 2, section 2.2). The EAG explained they did not include a separate cost for death because these are included in the costs of complications, death is a rare event, and because terminal care costs also apply to early deaths due to delayed diagnosis for people with false negative MRI results. However, it did a threshold analysis that found that the cost of complications in its base case would have to increase by more than 10,000% for the ICERs to reach a threshold of £30,000 per QALY gained if using LiverMultiScan to test for advanced NASH (see EAG addendum 2, section 2.2). The committee considered this analysis, as well as the suggested cost of complications submitted by Perspectum before the second committee meeting. The EAG noted that these costs come from a population with autoimmune hepatitis, who could have different risks associated with biopsy than a NAFLD population. The committee agreed that the impact of complications from biopsy was uncertain, but concluded that the costs would have to change by a large amount from the values used in the EAG's base case for the interventions to

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				be cost effective (see section 3.13 of the diagnostics guidance document).
14	Perspectum Ltd	3.1	*"The committee also noted that the risk of complications from liver biopsy is higher for people with very high BMI, who are at higher risk of having nonalcoholic fatty liver disease."* The weighted average of the utility values was taken from the Stevenson et al. (2012) HTA and the QALY decrement of 0.2 is stated as being *"equivalent to approximately 10 weeks with a utility of 0 or a year with a utility decrement of 0.2. The QALY value was **arbitrary**, but was assumed to be a value that would likely disfavour biopsy" (Stevenson et al., 2012).* **Why did the EAG not update this assumption given that the QALY decrement is one of the primary mechanisms of value for the technology under question (averting adverse events and associated disutilities)? How can a model utilising variables which are 'based on random choice or personal whim, rather than any reason or evidence be trusted and used to inform NICE clinical guidance?**	Thank you for your comment, which the committee has considered. The EAG stated that the model was populated with the best clinical and economic evidence available. It considered that the utility value associated with a biopsy complication used by Stevenson was extreme (utility decrement of 0.2, equivalent to 10 weeks of zero quality of life) and was biased against biopsy. As the most serious adverse event (death) was accounted for separately in the EAG model, the EAG considered that a more realistic assumption was to model one week with a zero quality of life (i.e., a utility decrement of 0.02) to reflect the effect on utility of adverse events not resulting in death (see EAG addendum 2, sections 2.3 and 2.6). The EAG did a threshold analysis that found that the QALY decrement from complications would have to increase by almost 20,000% to get an ICER of £30,000 per QALY gained if using LiverMultiScan to test for advanced NASH. The committee agreed that the impact of complications from biopsy was uncertain, but concluded that the costs would have to change by a large amount from the EAG's base case for the interventions to be cost effective (see section 3.13 of the diagnostics guidance document).
15	Perspectum Ltd		*"The committee also noted that the risk of complications from liver biopsy is higher for people with very high BMI, who are at higher risk of having nonalcoholic fatty liver disease."* There is a factual inaccuracy that has been published in the Stevenson et al. (2012) paper and therefore the Diagnostic Assessment Report. Please see the table below for more details. Values were taken from the section titled 'Adverse events related	Thank you for your comment, which the committee has considered. The EAG's diagnostics assessment report which contains this value (section 6.2.10) was made available to stakeholders for comment on 23rd June 2022. The EAG stated that the modified value provided by the stakeholder still generates what it considered to be a very

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr>
<td></td>
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<td>to each diagnostic test', page 67. The table below shows that the expected QALY decrement in the Stevenson et al. (2012) and the DAR are underestimated.

<table>
<tr><td></td><td>Percutaneous biopsy</td><td>Transjugular biopsy</td></tr>
<tr><td>Risk of causing an adverse event</td><td>0.72%</td><td>1.27%</td></tr>
<tr><td>QALY Decrement</td><td>0.2</td><td>0.2</td></tr>
<tr><td>Expected QALY decrement calculation based on figures</td><td>0.2*0.72% =0.00144</td><td>0.2*1.72% =0.00254</td></tr>
<tr><td>Expected QALY decrement presented in Stevenson et al. (2012) and the DAR</td><td>0.000142</td><td>0.000254</td></tr>
<tr><td>Difference from original</td><td>914%</td><td>900%</td></tr>
</table>

Why was this figure not validated when used in the model, especially given the conclusions from the model are heavily influenced by these values? The model needs to be updated with the correct values, with an opportunity for re-review, before guidelines are published.

Furthermore, given the errors in the provided EAG model, would it be possible to review the model used to justify inclusion of other diagnostic tests in the NAFLD guidelines?</td>
<td>high loss of QALYs from biopsy-related complications. It generated a scenario using the higher utility loss suggested (EAG addendum 2, section 2.6), which was considered by the committee at the second committee meeting. In this scenario, the ICERs remained above £100,000 per QALY gained for all strategies. It also did a threshold analysis that found that the QALY decrement from complications in its base case would have to increase by almost 20,000% to get an ICER of £30,000 per QALY gained if using LiverMultiScan to test for advanced NASH. The committee agreed that the impact of complications from biopsy was uncertain. It concluded that the costs and QALYs would have to change by a large amount from the values used in the EAG's base case for the interventions to be cost effective. It also concluded that the EAG's model and accompanying analyses were suitable for decision making (see sections 3.13 and 3.18 in the diagnostics guidance document).

A surveillance review of NG49 is ongoing. If this is updated, this diagnostics assessment of MRI-based technologies for assessing NAFLD guidance can be updated in the future if, for example, there are changes to relevant care pathways (which could include new treatments becoming available or changes to recommendations in NG49). The process of reviewing and updating existing guidance is described in the CHTE programme manual on the NICE website.</td>
</tr>
</table>

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THEME: Comments on modelling approach

Comment number	Name and organisation	Section number	Comment	NICE response
16	Perspectum Ltd	3.8	*"The EAG used a value of 0.03 quality adjusted life years (QALYs) per year for the disutility associated with the liver disease that was initially missed by the tests".* The 0.03 per year disutility is said to be taken from the NICE guidelines for assessment and management of NAFLD (NG49); however, this value cannot be found in the report. As such, it seems that this complex calculation and disutility value is not evidence based and cannot be ascertained from the description of its calculation. It is not clear what a disutility of 0.03 'per year' means in the context of a 6-month analysis. This was previously included in the response to the DAR but not properly addressed. What is the exact origin and precise interpretation of this 0.03 disutility value? How would a disutility of 0.03 occur if the patients are asymptomatic for the condition (As mentioned in the DCD, section 3.8)?	Thank you for your comment, which the committee has considered. As explained in the EAG's first addendum (section 1.3), the EAG stated the disutility could be interpreted as a loss of QALYs from delayed diagnosis, which could happen some time after a diagnosis is made. It explained that the source of the 0.03 disutility is the NG49 Appendices (p610, Table 62). In the model, the QALY loss is applied for 6 months, i.e., 0.03/2=0.015 (see EAG addendum 2, sections 2.3 and 2.10). The EAG also said that, if missing liver disease has no impact on health-related quality of life, then there would be no value to doing the test. However, it provided scenario analyses in which no disutility associated with missed liver disease was included in the base-case model, and cautioned that this should be considered exploratory analysis. It also highlighted that all ICERs exceeded £100,000 per QALY gained in this analysis (EAG addendum 1, Table 4). The committee concluded that the disutility associated with a missed diagnosis of liver disease is highly uncertain, but this should not be modelled as 0 (section 3.8 of the diagnostics guidance document).
17	Perspectum Ltd	3.8	*"The disutility over the 6-month time horizon of the model had a large effect on the incremental cost-effectiveness ratio"* As per the NICE (2022) DAP manual, "*The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between technologies being compared. Many technologies affect costs and outcomes over a patient's lifetime. This is particularly the case with treatments for chronic diseases. In such instances, a lifetime horizon for clinical and cost effectiveness is appropriate.*	Thank you for your comment, which the committee has considered. During the second committee meeting, the EAG clarified that the QALY loss from mortality due to biopsy is not limited to 6 months, but is applied as a one-time payoff relating to the whole period of life lost, and therefore is applied over a lifetime horizon. This is further explained in the diagnostics assessment report (section 6.2.2) and the EAG's second addendum (sections 2.3 and 2.10), in which it clarified that modifying the optimistic assumption that all people are given

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			A lifetime time horizon is also needed for any mortality component in order to quantify the implications of any differential survival effect between alternative technologies." The key value proposition for Liver*MultiScan* is to reduce the number of invasive biopsies. Liver biopsies have an associated mortality risk, acknowledged in the assessment report, and quantified for the economic modelling. This is however only integrated over a 6-month time horizon. The modelling approach is inconsistent with the NICE manual whilst also being clearly inappropriate for the decision problem. As per the NICE (2022) DAP manual, as there is a component of mortality being assessed, a lifetime horizon would have been more appropriate. The 6-month time horizon has also introduced a number of logical failings such as: 1. The impact of a 'false negative' on the QALYs gained. The report states a QALY loss of 0.03 'per year' which has no meaning within an analysis over 6-months. 2. The QALY loss associated with early mortality. It is not clear how this value has been calculated but it is unfeasibly low and clearly does not account for QALYs lost beyond the first 6 or 12-months of the analysis period. Previous analysis such as Stevenson et al. (2012); Younossi et al. (2019); Younossi et al. (2016); Phisalprapa et al. (2021); Klebanoff et al. (2019); Chongmelaxme et al. (2019); Pearson et al. (2016); Rind et al. (2020); Mahady et al., (2012); Phisalprapa et al. (2017); Tanajewski et al. (2017); Corey et al. (2016); Noureddin et al. (2020); and Zhang et al. (2015) have modelled similar decision problems over a lifetime horizon because of the clear conceptual and logical problems of adopting such short term time horizon.	a correct diagnosis at 6 months to a longer time frame would only increase the QALY loss associated with missed diagnosis from false negative test results, and reduce the cost effectiveness of the interventions. The committee recalled that several assumptions in the model were highly favourable to the MRI tests (see section 3.17 of the diagnostics guidance document). It concluded that the disutility associated with a missed diagnosis of liver disease is highly uncertain, but this should not be modelled as 0 (see section 3.8 of the diagnostics guidance document). For more detail on the disutility applied to missed disease from false negative results, please see NICE response to comment 16. The EAG provided an explanation of how the disutility applied to biopsy death was calculated in the diagnostics assessment report (section 6.2.10) and repeated this in its second addendum (section 2.3). The committee considered the potential impact of lifestyle interventions – please see NICE response to comment 1.

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			Additionally, Perspectum have provided additional information on treatment options of NAFLD, lifestyle intervention, that was ignored during the modelling process. For more information on this, please see comment [1]. **Perspectum request that the model is reconceptualised in line with published literature within the disease space.**	
18	Perspectum Ltd	3.14	*"Several assumptions made in the model need further consideration once more data is available"* The EAG did not complete a probabilistic sensitivity analysis which ignores the potential for different input parameters to interact in such a way simultaneously, that a change in them leads to a change in the overall ICER. The analysis shown in the addendum changed values by 20% and averaged across the outputs. The EAG admitted that the analysis showed the model was in fact non-linear but "*that any impact of non-linearity is not important for decision making"*. That in turn assumes that each individual model input could only be out by 20%. However, many of the model base-case inputs could be, and are likely to be, out by a far larger factor simultaneously. Taken together, there can be little confidence in the results of the current analysis. **Perspectum requests that the model is re-estimated, as many of the model assumptions and inputs are not evidence based, have been critiqued by committee members and NICE's internal team and contain factual inaccuracies (see previous comments). Guidelines should not rely on analysis that lacks confidence in its validity.**	Thank you for your comment, which the committee has considered. The EAG stated that its model was a single node decision tree (and was therefore linear) and felt that probabilistic sensitivity analyses were not relevant. It stated that probabilistic sensitivity analyses will not strengthen weak evidence or validate model assumptions (see EAG addendum 2, section 2.13). The committee concluded that although there was considerable uncertainty in the model's parameters, the EAG's model and accompanying analyses were suitable for decision making. It also recalled that several assumptions in the model were highly favourable to the MRI tests (see sections 3.17 and 3.18 of the diagnostics guidance document).

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THEME: Current availability of testing

Comment number	Name and organisation	Section number	Comment	NICE response
19	Perspectum Ltd	2.3	*"NICE's guideline on the assessment and management of non-alcoholic fatty liver disease advises to test for advanced liver fibrosis in people with NAFLD using the enhanced liver fibrosis (ELF) test."* Perspectum would like to reiterate a comment that was raised during the DAR commenting period which has not been addressed appropriately by the EAG. Perspectum would like to know how patients with NAFLD are being managed in CCGs that do not have access to TE or ELF tests. A cross sectional survey (Jarvis et al., 2021) found that only 25% of UK CCGs used TE and only 16% of CCGs used ELF tests to assess liver fibrosis. As per BSG guidelines (2021), routine liver enzyme blood tests are not recommended to rule out NASH. Therefore, the DCD needs to include management guidelines for CCGs that do not have access to tests such as TE or ELF. This further raises the issue of health inequalities if diagnostics or patient care is reliant on geographical area i.e., postcode lottery. MRI is available in all CCGs. This was previously included in the response to the DAR but not properly addressed. **How will NICE guidelines manage this lack of access given the NHS long term plan to advance equality and reduce health inequalities (NHS., 2018 NHS long term plan: Chapter 2: More NHS action on prevention and health inequalities: https://www.longtermplan.nhs.uk/online-version/chapter-2-more-nhs-action-on-prevention-and-health-inequalities/)?**	Thank you for your comment, which the committee has considered. It is important to note that providing management guidelines for commissioning groups is beyond the scope of diagnostics assessments, which is intended to assess the clinical and cost effectiveness of a new technology. During scoping, clinical experts advised that using an MRI-based test as an initial assessment for liver health (that is, before or as an alternative to currently used tests) was unlikely to be feasible in the NHS because of available MRI capacity (scope, section 4). The committee further highlighted substantial barriers to increasing use of MRI scans in the NHS (see section 3.3 in diagnostics guidance document). The population for this assessment includes people with intermediate or discordant results from previous fibrosis testing, without specifying that this population must have been tested with transient elastography or ELF. As described in section 2.4 of the diagnostics consultation and guidance documents, the British Society of Gastroenterology (BSG) guideline on NAFLD recommends testing for fibrosis in people with NAFLD using the NAFLD fibrosis score (NFS) or FIB-4. If these scores indicate an intermediate risk, transient elastography or the ELF test can be used to further clarify the diagnosis. If the non-invasive tests are not able to exclude advanced fibrosis, the BSG recommends that liver biopsy is considered. During the second committee meeting, clinical experts commented that tests such as FIB-4 and the NFS are routinely available in the NHS. The population described in the comment (where transient elastography or ELF are not available) and only test results such as FIB-4 are available, and results are considered indeterminate, or

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				discordant with any other information available test results or information, would therefore fall within the scope of the assessment. Notwithstanding the above, the EAG's systematic review of clinical evidence did not only look for people who had previously had TE or ELF, but used broad inclusion criteria (people with NAFLD for whom advanced fibrosis or cirrhosis had not yet been diagnosed; diagnostics assessment report section 5.2). So, the gaps in evidence identified by committee remain for people without access to these tests. In particular, uncertainty about how the result of the LiverMultiScan would change care or people's adherence to lifestyle advice or interventions would still remain a considerable uncertainty regardless of what previous tests had been done prior to the test being used.
20	Perspectum Ltd	2.3	*"NICE's guideline on the assessment and management of non-alcoholic fatty liver disease advises to test for advanced liver fibrosis in people with NAFLD using the enhanced liver fibrosis (ELF) test."* Following on from Comment [19], the EAG's response to our initial comment (no. 14) stated that "*The EAG is not aware of any published literature that provides this information* [i.e., how are patients with NAFLD being managed in CCGs that do not have access to any of these tests]*"*; however, they did not consider the NHS reports and slides that were submitted (from Homerton University Hospital NHS Trust, West Hertfordshire Hospitals NHS Trust and East and North Hertfordshire CCG, publicly available) or the published literature on current clinical practice for diagnostic testing of NAFLD/NASH. Rinella et al (2022) collected cross sectional survey data from 226 US based healthcare professionals and Ratziu et al (2022) surveyed physicians who care for NAFLD patients in 8 countries worldwide, including the	Thank you for your comment, which the committee has considered. The focus of the assessment is on NHS practice and to support recommendations for the NHS, therefore, modelling variations in practice across the world was not considered. Comments received during consultation on the diagnostics assessment report are available to the committee for their consideration. Committee noted that there is variability in practice. A statement has been added to section 2.2 of the diagnostics guidance document that specific tests and pathways used vary across the country. A committee member noted that, under the diagnostic and monitoring algorithm proposed by Perspectum, people would be assessed by LiverMultiScan every 6 months to 3 years, which could result in a number of additional MRI scans being

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			UK. Regarding the material not published in peer reviewed literature, Perspectum feel that NICE should consider information that has been submitted by UK clinical experts, especially if it can help alleviate health inequalities and increase the quality of patient care. These audits of hepatology services and pathways provide an insight into real world practice that has been ignored by the EAG. Dr Mohamed Shariff (Consultant Gastroenterologist and Hepatologist, West Hertfordshire Hospitals NHS Trust) stated that the ELF test is not only expensive but temporarily unavailable, leading them to **ignore NICE guidance based on test availability** (Developing a Fatty Liver Service (slide show)). Additionally, Jarvis and Hanratty (2016) published an editorial in the British Journal of General Practice stating that "*The NICE recommendation for the use of the ELF test in NAFLD poses similar challenges. ELF is currently unavailable in most NHS laboratories. If it was to become available, and used on even half of the patients estimated to have NAFLD, this would mean 5 million tests conducted annually, the majority of which would need to be repeated on a 3-yearly basis."* This was previously included in the response to the DAR but not properly addressed. **How does NICE/EAG justify ignoring published literature and real-world evidence from UK clinical experts highlighting the gaps in, and barriers to implementing, existing NICE guidelines? These issues highlight the need for alternate and accessible non-invasive tests.**	needed comparable to the number of ELF tests highlighted by the Jarvis and Hanratty paper included in the comment.
21	Perspectum Ltd	2.11	"*Following testing as described in sections 2.2 to 2.4, in the absence of MRI-based testing, no other tests would be done before decision to do a biopsy or any other care decision"*. In line with comment [19] above, if patients cannot access ELF, FIB-4 or TE based on geographical inequalities, it can be inferred that patients will undergo more biopsies as there will be no initial	Thank you for your comment, which the committee has considered. During scoping, clinical experts advised that using an MRI-based test as an initial assessment for liver health (that is, before or as an alternative to currently used tests) was unlikely to be feasible in the NHS because of available MRI

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			test to risk stratify them. Given the complications and other issues associated with biopsy that arose during EAG analysis (anxiety etc.), recommending MRI-based technologies across the UK would provide a solution to these inequalities. This was previously included in the response to the DAR but not properly addressed. **Given that not having access to initial fibrosis testing is effectively equivalent to it being unsuitable or not working, the EAG should add 'those who do not have access to initial fibrosis testing' (TE: 75% of CCGs, ELF: 84% of CCGs, (Jarvis et al., 2021)) to those 'with indeterminate or discordant results from previous fibrosis testing' and 'when transient elastography or acoustic radiation force impulse elastography (ARFI) is unsuitable or has not worked' and update the model accordingly.** This update to the model would materially impact the results and ensure it is reflective and supportive of current practice and availability across NHS trusts, rather than an "idealised" trust with all recommended tests available.	capacity (scope, section 4). The committee further highlighted substantial barriers to increasing use of MRI scans in the NHS (see section 3.3 in diagnostics guidance document). The population for this assessment includes people with intermediate or discordant results from previous fibrosis testing, without specifying that this population must have been tested with transient elastography or ELF. As described in section 2.4 of the diagnostics consultation and guidance documents, the British Society of Gastroenterology (BSG) guideline on NAFLD recommends testing for fibrosis in people with NAFLD using the NAFLD fibrosis score (NFS) or FIB-4. If these scores indicate an intermediate risk, transient elastography or the ELF test can be used to further clarify the diagnosis. If the non-invasive tests are not able to exclude advanced fibrosis, the BSG recommends that liver biopsy is considered. During the second committee meeting, clinical experts commented that tests such as FIB-4 and the NFS are routinely available in the NHS. The population described in the comment (where transient elastography or ELF are not available) and only test results such as FIB-4 are available, and results are considered indeterminate, or discordant with any other information available test results or information, would therefore fall within the scope of the assessment.

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THEME: Impact of wait times

Comment number	Name and organisation	Section number	Comment	NICE response
22	Perspectum Ltd	3.3	"*Radiologist experts highlighted that wait times for MRI scans in the NHS are already long, with services working at full capacity.*" **Perspectum feel that not all viewpoints of the committee are captured in this section**. When discussing MRI capacity within the NHS, it was raised that introducing Liver*MultiScan* might not have as big an impact on radiology services as the number of Liver*MultiScan* appointments would be incredibly small compared to all MRI procedures performed in the NHS. Freedom of Information Requests have been submitted to numerous UK trusts requesting information regarding MRI usage and liver biopsy occurrence. In addition, Community Diagnostic Centres are being launched across England to help achieve: 1. Earlier diagnosis for patients through easier, faster, and more direct access to the full range of diagnostic tests needed to understand patients' symptoms including breathlessness, cancer, ophthalmology 2. A reduction in hospital visits which will help reduce the risk of COVID-19 transmission **3. A reduction in wait times by diverting patients away from hospitals, allowing them to treat urgent patients, while community diagnostic centres focus on tackling backlog** 4. A contribution to the NHS's net zero ambitions by providing multiple tests at one visit, reducing the number of patient journeys and helping to cut carbon emissions and air pollution (Gov.uk., 2021 https://www.gov.uk/government/news/40-community-diagnostic-centres-launching-across-england). Perspectum, in partnership with Oxford University Hospitals NHS Foundation Trust (OUH), has opened one of these Community Diagnostic Centres at their head office and will contribute to	Thank you for your comment, which the committee has considered. The EAG commented that it had looked for data on the impact of the MRI tests on time to diagnosis but was unable to find any. The committee concluded that there was no evidence to demonstrate that adding MRI to the NAFLD pathway would reduce time to diagnosis, and while there was the potential for this to be a benefit of testing, the size of any benefit was highly uncertain. The extent of any benefit may depend on what actions could be taken on the basis of MRI tests alone. The extent of impact on QALYs of a quicker diagnosis from testing is also uncertain (see sections 3.8 and 3.12 of the diagnostics guidance document). The key uncertainty about how the results of a LiverMultiScan would change care or people's adherence to lifestyle advice or interventions (as described in sections 3.2 and 3.5) mean that any impact of receiving an earlier diagnosis resulting from use of the test would remain uncertain.

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			delivering up to 800,000 additional tests in the UK in 2022 (Oxford University Hospitals NHS Foundation Trust., 2021 https://www.ouh.nhs.uk/news/article.aspx?id=1678&returnurl=/default.aspx&pi=0) No data or evidence was provided by the committee on the scale of potential impact; therefore, additional research should be performed and included in the model as a sensitivity analysis.	
23	Perspectum Ltd	3.9	*"The committee recalled its conclusion that more MRI testing in NAFLD would have a significant impact on demand for MRI."* Please see comment [22]. **Given the absence of data presented to the committee to evidence this claim, Perspectum have submitted FOI requests to UK trusts to obtain real world data on MRI scan use over the past 5 years. Has the EAG/NICE made attempts to obtain this information as well?**	Thank you for your comment, which the committee has considered. It is beyond the capacity of the EAG to conduct extensive surveys of hospitals across the UK to support their work. Any such data that is published would be identified in the systematic literature review done. Stakeholders are welcome to submit any such data that supports claims made about potential impact of the technologies. Data provided to committee by Perspectum in advance of the second committee meeting on waiting times in gastroenterology departments obtained from the NHS website was presented during the second committee meeting and considered by the committee.
24	Perspectum Ltd	3.11	*"Clinical and patient experts stated that their experience of wait times for liver biopsy were much lower than suggested by the company, between 2 days and 6 months."* As mentioned in the DCD, there is not a consideration within the model for the considerable wait list for some people to access liver biopsy in the UK, nor to the fact that a large population may refuse to have a liver biopsy. **The model should be revised to account for biopsy waiting time, for example by extending the time horizon; especially given that a 6-month waiting time for a biopsy would mean a**	Thank you for your comment, which the committee has considered. The committee considered the information submitted by Perspectum on the highest average waiting times for gastroenterology appointments and treatment, obtained from the NHS website. The committee concluded that there was no evidence to demonstrate that adding MRI to the NAFLD pathway would reduce time to diagnosis, and while there was the potential for this to be a benefit of testing, the size of any

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			missed diagnosis using the current model (6-month time horizon).	benefit was highly uncertain (see section 3.12 of the diagnostics guidance document). Regarding people who choose not to have a biopsy, please see the NICE response to comment 11.
25	Perspectum Ltd	3.11	*"The committee also notes that there are currently significant waiting times for MRI, and that introduction of MRI to the NAFLD care pathway could further increase the wait".* Please see comment [22]. **No data or evidence was provided by the committee on the scale of potential impact; therefore, additional research should be performed and included in the model as a sensitivity analysis.**	Thank you for your comment, which the committee has considered. Given the lack of evidence identified on the potential impact of adding MRI to the care pathway, the committee based their considerations on expert radiologist advice (see section 3.3 of the diagnostics guidance document). Please see the NICE response to comment 22 for more detail.

THEME: Differences between MRI-based tests

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26	Perspectum Ltd	3.1	*"MRI may also not be suitable for people with a very high body mass index (BMI) because of the size of the scanner bore".* MRE has high failure rates (Ranging from 3.5% at 1.5T and 15.3% at 3.0T, (Wagner et al., 2017; Liang and Li, 2020; Hsu et al., 2019), especially in obese patients where tests are not possible due to body habitus. Additionally, there are wide indeterminate zones between threshold values for ruling out or ruling in the presence of	Thank you for your comment, which the committee has considered. The EAG did a scenario analysis using the failure rate found by Wagner et al. 2017 in 3.0T scanners, which can be found in section 2.5 of the EAG's second addendum. It stated that the conclusions that can be drawn are not different from the EAG's base case. The committee acknowledged that ultrasound-based tests such as transient elastography and acoustic radiation force impulse elastography (ARFI) are not suitable for some people, due to increased failure rates in

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			advanced fibrosis (Lazo et al., 2008; McDonald et al., 2018; Newsome, et al., 2018) even when used alongside a blood test like ELF or FIB-4 (Boursier, Sanyal and Ratziu, 2020). Failure rates at 3.0T are higher than the percentage of people unable to complete an MRI scan (3.5%, unpublished RADIcAL 1 data). **NICE/EAG should explicitly comment on the high failure rates and availability of existing tests to provide context when discussing potential limitations of new diagnostic tools. It should be added to the DCD that Liver*MultiScan* is not confounded by body habitus and BMI unlike ultrasound diagnostics and MRE (Imajo et al., 2021; Wagner et al., 2017 and Liang and Li, 2020).**	people with high BMI, particularly with central obesity (see section 3.4 of the diagnostics guidance document).
27	Perspectum Ltd	3.4	*"Clinical experts considered that MRI-based tests could have particular benefit for the NHS when transient elastography or ARFI has not worked or is unsuitable."* Perspectum agrees with this statement, furthermore while Liver*MultiScan* is suitable for obese/high BMI patients (Imajo et al., 2021), studies have shown that MRE has increased technical failure rates in patients with high BMI and/or liver iron deposition (Wagner et al., 2017; Liang and Li., 2020). The aforementioned benefit of LiverMultiScan has also been highlighted in the American Association of Clinical Endocrinology (AACE) guidelines for NAFLD/NASH following FIB-4 or TE results (Cusi et al., 2022) along with AIM Radiology Business Manager guidelines (2022). The latter state that Liver*MultiScan* is medically necessary for diagnosis and management of ANY of the following: 1. NAFLD in patients with high risk of cirrhosis due to advanced age, obesity, diabetes, or ALT level more than twice the upper limit of normal 2. Other established chronic liver diseases when ultrasound elastography cannot be performed or is nondiagnostic	Thank you for your comment, which the committee has considered. The 2 technologies have been described in sections 2.8 to 2.11 of the diagnostics consultation and guidance documents. The committee agreed that MRE and LiverMultiScan required further differentiation, and as such the research recommendations and committee considerations have been reported separately (please see sections 1.2, 3.14 to 3.16, 3.19 to 3.21 and 4.1 and 4.2 in the diagnostics guidance document).

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			3. Iron overload in hemochromatosis **Perspectum request that Liver*MultiScan* and MRE are differentiated in this section as MRE requires external mechanical stimulation that is attenuated by subcutaneous fat which impacts its performance in obese patients, unlike Liver*MultiScan*.**	
28	Perspectum Ltd	3.7	*"Clinical experts reiterated that the MRE test was likely to be most useful in populations when non-invasive tests for fibrosis (such as transient elastography) could not be used, for example because of high BMI."* Please see comment [26] which highlight flaws with MRE in high BMI patients with NAFLD and NASH. **NICE/EAG should explicitly comment on the high failure rates of existing tests to provide context when discussing potential limitations of new diagnostic tools. It should also be included that Liver*MultiScan* is not confounded by body habitus and BMI unlike ultrasound diagnostics and MRE (Imajo et al., 2021; Wagner et al., 2017 and Liang and Li, 2020).**	Thank you for your comment, which the committee has considered. The committee acknowledged that ultrasound-based tests such as transient elastography and acoustic radiation force impulse elastography (ARFI) are not suitable for some people, due to increased failure rates in people with high BMI, particularly with central obesity (see section 3.4 of the diagnostics guidance document). The EAG used the failure rate for LiverMultiScan from Eddowes et al. 2018 for their analysis of both LiverMultiScan and MRE (diagnostics assessment report section 6.2.7; EAG addendum 1, section 1.4). The EAG did a scenario analysis using the failure rate for MRE found by Wagner et al. 2017 in 3.0T scanners, which can be found in section 2.5 of the EAG's second addendum. It stated that the conclusions that can be drawn are not different from the EAG's base case.
29	Perspectum Ltd	3.9	*"The EAG's model included costs of doing MRI, but not any costs for changes to NHS infrastructure that may be needed for more MRI use."* While Liver*MultiScan* requires no additional capital purchases or infrastructure to enable use on existing MRI scanners, MRE requires purchase of an external driver (mechanical stimulator). The Resoundant website advertises an acquisition cost of over $100,000 (£84,000) (https://www.resoundant.com/radiology)	Thank you for your comment, which the committee has considered. The intervention technologies have been described in sections 2.8 to 2.11 of the diagnostics consultation and guidance documents, which includes a description of the hardware requirements for MRE. Costs of acquiring MRE were used in the EAG's model, and are based on those provided by Resoundant in response to a NICE request for information. The EAG noted that the cost of MRE is not set

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			which is substantially higher than the value quoted in the EAG committee papers. **This additional capital expenditure should be captured in the EAG model and a clearer distinction between MRE and Liver*MultiScan* should be made.**	by Resoundant, but rather by individual MRI manufacturers, and is therefore likely to vary. Full details of how the EAG calculated the acquisition cost can be found in its first addendum, section 1.4. The EAG noted that, using this cost, MRE was not a cost-effective option at a threshold of £30,000 per QALY, and increasing this cost would not change the conclusions. Cost-effectiveness estimates were provided with and without an acquisition cost for MRE hardware (EAG addendum 1, tables 11 and 12). Clinical experts in the committee stated that MRE is not widely available in the NHS, so including the acquisition cost would be more realistic. The committee concluded that the cost of MRE was a significant factor in whether or not the test could be cost effective, and that the true cost was highly uncertain (see section 3.15 of the diagnostics guidance document).
30	Perspectum Ltd	3.14	*"Clinical experts commented that MRE could have a role in the NHS if used when previous tests such as transient elastography or ARFI either could not be done, had not worked, or gave discordant results, in line with the scope population".* MRE faces similar problems as TE such as an increased technical failure rates in patients with high BMI and/or liver iron deposition, (Wagner et al., 2017) – **Did the committee consider these factors, rather than just the results from the cost effectiveness analysis?** MRE has also been shown in a systematic review and meta-analysis (Castera et al., 2009) to have failed tests in 25% of attempts. Another study (Caussey et al., 2018) found that BMI was significantly associated with discordance between MRE and TE in diagnosis of fibrosis stage. Please see comment [26] for additional studies.	Thank you for your comment, which the committee has considered. The EAG noted that the MRE failure rate of 25% highlighted by Perspectum Ltd was reported in a study published in 2009, and more recent evidence shows lower failure rates (see EAG addendum 2, section 2.5). The EAG used the failure rate for LiverMultiScan from Eddowes et al. 2018 for their analysis of both LiverMultiScan and MRE (diagnostics assessment report section 6.2.7; EAG addendum 1, section 1.4). The EAG did a scenario analysis using the failure rate found by Wagner et al. 2017 in 3.0T scanners, which can be found in section 2.5 of the EAG's second addendum. It stated that the conclusions that can be drawn are not different from the EAG's base case.

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THEME: Use of MRI tests for children or young people

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31	Perspectum Ltd	2.7	The committee acknowledged that Liver*MultiScan* may be relevant in the care of a child, despite this not being the population presented in the model as performing biopsy on children is considered unsustainable. **Perspectum feel this should be acknowledged in the public facing reports. Could we also get clearer justification on why performing a biopsy on an adult is more acceptable than on a child?**	Thank you for your comment, which the committee has considered. Comment from the Children's Liver Disease Foundation (CLDF) stated that biopsies on children are normally done under general anaesthetic, which increases the risk associated with the procedure (see comment 33). Children were highlighted as a group that could particularly benefit from access to more non-invasive options for testing in considerations for further research (see sections 3.1 and 3.22 of the diagnostics guidance document). The CLDF also highlighted that guidelines from the British Society for Paediatric Hepatology Gastroenterology and Nutrition contain guidance on when a liver biopsy is acceptable for children – this has been added to the diagnostics guidance document in section 2.5.
32	Children's Liver Disease Foundation	2.4	We note the BSG guidelines. We want to highlight the British Society for Paediatric Hepatology Gastroenterology and Nutrition guidelines for NAFLD August 2020 developed following a Tri-Centre Specialist Paediatric Audit LSG_UK-Fatty-Liver-Guideline-August-2020.pdf (bspghan.org.uk) where biopsy is indicated in NAFLD diagnosis in children.	Thank you for your comment, which the committee has considered. Reference to this guidance has been added to the diagnostics guidance document in section 2.5.
33	Children's Liver Disease Foundation	General	CLDF is not in a position to challenge the scientific opinion of the efficacy and cost effectiveness of these technologies. We are also aware that the focus of this appraisal was diagnosis/care in the adult population. As a children's charity we have watched the development of these technologies with great interest and want to champion effective non-invasive diagnostics for our cohort. We know only too well the huge impact biopsies have on small children, their experience of care and the impact on families. There is also increased risk as in children the biopsies take place under general anaesthetic (with additional NHS costs and family	Thank you for your comment, which the committee has considered. The focus of this assessment included children as an important subgroup (please see scope, section 6). Unfortunately a lack of data in this population prevented the EAG from exploring this fully (see diagnostics assessment report, Appendix 5). Section 3.1 of the diagnostics guidance document has been updated to reflect that the committee considered the

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			worry). Any effective technology that can reduce the need for biopsy in the diagnosis and care of children will have a benefits far beyond the NHS costs involved. We also have watched the prevalence of NAFLD increasing in children and the data emphasising that 34-38% of obese children are likely to have biopsy proven NAFLD is alarming. Anything that can be done to improve diagnosis for children with NAFLD without the use of invasive procedures should be a priority. We feel it is only through effective diagnosis that a journey to family management of the condition and suitable care can be provided. We also feel it is important to highlight that NAFLD is a diagnosis with significant health implications but also stigma, peer judgement, mental health/ bullying issues and parental guilt.	increasing prevalence of NAFLD in children, the potential benefits of non-invasive technologies for diagnosing liver conditions, and the higher risk of liver biopsy for children. Children were highlighted as a group that could particularly benefit from access to more non-invasive options for testing in considerations for further research (see section 3.22 of the diagnostics guidance document).

THEME: General comments on draft guidance and guidance process

Comment number	Name and organisation	Section number	Comment	NICE response
34	Perspectum Ltd	1	Perspectum feel there is a fundamental lack of forward thinking and unnecessarily narrow approach to the guidelines for NAFLD that appears to be driven by a very static approach to the economic modelling, outweighing a practical view on the care pathway and issues that might arise, for example: • Having no means of knowing and modelling when a patient has progressed from NAFL to NASH. Please see comments [2] and [37] for more information on the importance of differentiating NAFL from NASH. • Ignoring the clear patient preference to non-invasive biopsy alternative. Please see comment [11] for more information • Not considering the wait times for biopsy. Please see comment [23] for more information.	Thank you for your comment, which the committee has considered. Responses to the points raised here are addressed in full alongside the corresponding comments elsewhere in this document.

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			• The lack of consideration or promotion of effective treatment options such as lifestyle intervention. Please see comments [1] for more information • Not considering the possibility that pharmacotherapies could come to market in the near future. Please see comment [3] for more information. Ignoring the comprehensive modelling performed for NICE in 2016 (NG49) which shows NITs for NAFLD and advanced fibrosis dominating biopsy. See comments [2] and [5] for more information.	
35	Perspectum Ltd		Perspectum are concerned that despite providing detailed information and data relevant to this guideline review, a lot of this is has been improperly discounted and ignored. We feel that clinicians, patients and others using this guidance should not be disadvantaged because the EAG will not accept data provided, especially when the reason for not accepting this data is as illogical as *"Thank you for the information about the threshold. It is not possible to update the EAG report at this stage of the process".* We feel it is unethical and nonsensical to refuse to update the EAG report with relevant information provided **during the review process**. Within this commenting document there are 8 instances where points from the DAR commenting period have had to be repeated as Perspectum feel that they were not addressed appropriately. Unfortunately, if they are not addressed within the next response period, Perspectum will have option but to escalate our concerns. **If the data will not be used by NICE/EAG to help improve patient care, we would like to provide feedback that can help improve technology assessment programmes in the future. Can we get assurance that our feedback will be addressed appropriately? What is the process for raising a formal complaint and investigation?**	Thank you for your comment, which the committee has considered. The final diagnostics assessment report (DAR) is circulated to registered stakeholders for comment. This is not a review period but rather commentary on the final report. The EAG are therefore not able to update the DAR once it has been circulated to stakeholders. Any identified errors in the report can be corrected by an erratum (see the EAG erratum for some corrections in this assessment). Multiple addenda have been produced to address new data that stakeholders have submitted, and to respond to requests for further analysis). Stakeholder comments on the DAR are circulated to the Diagnostic Advisory Committee in advance of the first committee meeting for consideration in decision-making. If stakeholders believe there are factual inaccuracies in the guidance or if there has been a breach of NICE's process, they can raise a resolution request as described in the process manual, as described in the diagnostics programme manual – please see section 8.

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36 (part 2)	Perspectum Ltd	1.2	…Other technologies, for example, OncoType DX (GD10, updated version GD34) relied on the small Holt et al., (2013) study of potential clinical utility as evidence during the NICE assessment programmes for guideline inclusion. This study showed a change in decision making in 38/142 (26.8%) patients. **Why have other technologies received favourable opinion in guidelines/DAP/MTEP based on similar/lower levels of evidence? Please provide more justification for the discordant approach to assessment.**	Thank you for your comment, which the committee has considered. The cited Holt et al. study was used in NICE diagnostics guidance (DG) 34 in addition to several other studies (described in table 128 on page 363 of the DG34 diagnostics assessment report) to inform the EAG's economic model for that assessment, specifically what proportion of people received chemotherapy based on risk classification from the assessed test. The size of evidence base is therefore larger than suggested in the comment and includes 4 UK-based studies (described on page 362 of the diagnostics assessment report for that topic). For this guidance, only the RADIcAL1 study gave direct evidence on the impact of MRI-based tests on decisions about care, which was not published. The committee noted that a relatively small number of people had a liver biopsy (55 out of 802), and that the authors of the study report commented that the low number of people having biopsies was likely because there are no current treatment options for NASH. Therefore, unless the clinician suspects advanced fibrosis, the clinical management will be the same for simple fatty liver and NASH. A lower proportion of people had 'unnecessary' biopsies (defined by the study authors as biopsy with a negative NASH result) in the LiverMultiScan trial arm (9 out of 22, 41%) compared with the standard care arm (16 out of 31, 52%), although this was not statistically significant (EAG calculated odds ratio 0.65, 95% confidence interval 0.22 to 1.96). The EAG judged the risk of bias for the study as high (see the diagnostics assessment report for this assessment, page 57, for further detail).

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				Notwithstanding the above, recommendations in NICE diagnostics assessment guidance are not only based on the extent of evidence, but also considerations of cost effectiveness. The committee concluded in DG34 that Oncotype DX was likely to be cost effective (see section 5.20 of the diagnostics guidance for that topic). Based on the EAG's base case model for the current assessment, which estimated a decrease in biopsy use similar to that shown in the only source of data identified (RADIcAL1; see section 3.14 of the diagnostics guidance document), LiverMultiScan was dominated or had much higher ICERs than are usually considered acceptable.
37	Perspectum Ltd	3.2	"*The committee concluded that, based on current practice, the impact of diagnosis of NAFLD on clinical practice management is very uncertain.*" Perspectum is concerned by the suitability of some of the clinical experts on this committee since statements like the above are not representative of the NICE recommendations, BSG guidelines (BSG, 2021), other non-UK guidelines Including the EASL-EASD-EASO Clinical Practice Guidelines (2016) and many other clinical experts (anecdotal experience). **How is the suitability of committee members assessed, and how do you ensure they are familiar with existing NICE recommendations and relevant clinical guidelines?** NICE guidelines include recommendations for NHS England at national level and are therefore committee opinions should be representative at this scale.	Thank you for your comment, which the committee has considered. Specialist committee members for NICE diagnostics appraisals are chosen through an open and competitive recruitment process, full details of which can be found in section 4.2.2 of the 2011 diagnostics programme manual. NICE did not have concerns about the suitability of the specialist committee members chosen after completing this process.
3 (part 2)	Perspectum Ltd	3.5	**…What is the process for Perspectum to escalate these significant concerns with the EAG's analysis in order to gain a fair and reasonable assessment of our technology and ensure the resulting guidelines best reflect current evidence?**	Thank you for your comment, which the committee has considered. If stakeholders believe there are factual inaccuracies in the guidance or if there has been a breach of NICE's process, they can raise a resolution request as described in the

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				process manual, as described in the 2011 diagnostics programme manual – please see section 8.
38	Resoundant		We would also encourage (and look forward to working with) the EAG to work with other NHS colleagues to create MRI reimbursements that better reflect exams that do not require the same amount of time and resources of traditional/full MRI protocols. For example, a standard MRE+PDFF exam can take just 5 minutes of scan time, compared to a typical abdominal MRI exam which can often take 30-45 minutes. This reduction of resources needed could be reflected through a lower reimbursement for the MRE+PDFF exam as compared to the full abdominal MRI exam. This would help further the cost-effectiveness case for non-invasive technologies such as MRE while better reflecting reue costs to the healthcare system.	Thank you for your comment, which the committee has considered.
39	Children's Liver Disease Foundation	1.2	CLDF fully endorses the need for further research to determine the accuracy of LiverMultiscan and MRE for assessing NAFLD and how decisions affect care and treatment. It is clear that the view not to recommend has been significantly affected by confusion in this area and the small range of specific research evidence.	Thank you for your comment, which the committee has considered.
40	Children's Liver Disease Foundation	2.3 and 2.4	CLDF has recently been asked our opinion on the need to update the NICE NAFLD guidelines, we feel very strongly that this work should be undertaken as they are out of date. We hope that the outcome of that process should it happen will be helpful in further consideration of these technologies.	Thank you for your comment, which the committee has considered. A surveillance review of NG49 is ongoing. If this is updated, this diagnostics assessment of MRI-based technologies for assessing NAFLD guidance can be updated in the future if, for example, there are changes to relevant care pathways (which could include new treatments becoming available or changes to recommendations in NG49). The process of reviewing and updating existing guidance is described in the CHTE programme manual on the NICE website.

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41	Oxford AHSN [web comment]	[Has all of the] relevant evidence been taken into account?	Yes all the relevant evidence has been taken into account	Thank you for your comment, which the committee has considered.
42	Oxford AHSN [web comment]	[Are the summaries] of clinical and cost effectiveness reasonable interpretations of the evidence?	Summaries of clinical and cost-effectiveness are reasonable [interpretations] of the evidence and agreed that MRI-based technologies for assessing non-alcoholic fatty liver disease in the NHS in England can be helpful	Thank you for your comment, which the committee has considered.

THEME: Suggestions of further data for consideration

Comment number	Name and organisation	Section number	Comment	NICE response
36 (part 1)	Perspectum Ltd	1.2	*"There is only 1 study on the effect of using LiverMultiScan on the number of liver biopsies, which is of low quality."* They study being referred to, RADIcAL-1, was a multi-centre real-world evidence study of the impact of LiverMultiScan on NAFLD care, including utilisation of liver biopsy, across Europe (Tonev et al., 2020, NCT03289897). Perspectum in no way influenced the number of biopsies performed as part of standard of care and thus the results reflect **actual** clinical practice. The study revealed	Thank you for your comment, which the committee has considered. The EAG assessed the RADIcAL1 trial as having a high risk of bias due to high concerns with the randomisation process and missing outcome data, and some concerns regarding deviations from intended interventions and measurement of

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			that biopsies are often not used in clinical practice with a resulting sub-optimal diagnostic certainty. This highlights the need for improved non-invasive tools to avoid poor management of patients. High diagnostic uncertainty can result from a reliance on less sensitive (or inaccessible) technologies recommended in current guidelines. One of the committee members queried the validity of these results, stating that it was not representative of clinical practice. This opinion is not reflected in recently published literature where biopsy is only performed in 56% of patients to confirm NASH diagnosis (Rinella et al., 2022) and 17% of UK clinicians will wait for biopsy requirement to be lifted before performing the invasive procedure in order to prescribe an approved NASH drug (Ratziu et al., 2022). Furthermore, the member's institution has been non-responsive to a Freedom of Information Request we submitted to ascertain the true number of liver biopsies performed in their trust…	the outcome (see appendix 11 of the diagnostics assessment report). The committee considered evidence from RADIcAL1 on the impact of LiverMultiScan on biopsy use (see section 3.6 of the diagnostics guidance document). A lower proportion of people had 'unnecessary' biopsies (defined by the study authors as biopsy with a negative NASH result) in the LiverMultiScan trial arm (9 out of 22, 41%) compared with the standard care arm (16 out of 31, 52%), although this was not statistically significant (EAG calculated odds ratio 0.65, 95% confidence interval 0.22 to 1.96). The EAG did a scenario analysis using the sensitivity and specificity data provided by Perspectum for the detection of advanced NASH from the RADIcAL1 trial, which produced an ICER of £317,104 per QALY gained (see EAG addendum 2, section 2.1). The committee considered that further data on test accuracy would be highly beneficial to help estimate true test accuracy, but also that studies which showed how well LiverMultiScan results predicted later clinical events could be used as an alternative to assess test performance (see section 3.19 in the diagnostics guidance document).
43	Perspectum Ltd	3.4	*"However, no diagnostic accuracy data was found for the MRI tests in this population."* Although no diagnostic accuracy data was found for the specific subset of patients in whom TE failed or was unreliable, a publication showing that cT1 predicted clinical outcomes, equivalent to biopsy was submitted to the EAG. Using an intention to treat analysis in patients who failed to obtain TE results, or whose TE result was unreliable, cT1 predicted outcomes, but TE did not (Jayaswal et al., 2020). This evidence highlights the utility of Liver*MultiScan* in exactly this population.	Thank you for your comment, which the committee has considered. The EAG considered all three of the suggested papers in their clinical effectiveness review (see section 5 of the diagnostics assessment report). It has further clarified how these publications were assessed in section 2.9 of the second addendum. The Jayaswal paper did not report 2x2 data. It also included multiple liver disease aetiologies (people with NAFLD, alcohol-related liver disease and viral hepatitis), and the

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			All publications including Liver*MultiScan,* TE or ARFI and biopsy include a substantial number of patients for whom TE or ARFI failed with no indication of a differing performance of Liver*MultiScan* in these patients (Imajo et al., 2021, Jayaswal et al., 2020, Pavlides et al., 2017 (where reliable TE results were only available in 38/71 patients)). **Perspectum requests that NICE/EAG consider data from these publications with biopsy-paired Liver*MultiScan* data in patient populations with substantial failure of TE or ARFI.**	study did not report results for NAFLD separately (see section 3.19 of the diagnostics guidance document). The Imajo and Pavlides papers were included in the EAG's clinical effectiveness review, see, for example, Forest plots in figure 4 of the diagnostics assessment report. The EAG did a scenario analysis using its base case (diagnostics assessment report, Section 6.2.14) which showed that the sensitivity and specificity of LiverMultiScan could be 100% and the ICER would still be above £30,000 per QALY gained. Section 3.4 of the diagnostics guidance document has been amended to read, "Some studies identified included this population, but diagnostic accuracy data was not reported separately from the overall population."

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THEME: Suggestions for clarifications in the guidance

Comment number	Name and organisation	Section number	Comment	NICE response
44	Perspectum Ltd	3.1	*"The committee noted that liver biopsy can also have issues such as sampling error (that is, biopsy can only sample a small part of the liver, which may miss affected areas)."* **Perspectum feel that the DCD should be more transparent regarding liver biopsy. The DCD should define "*a small part of the liver"* as 1/50,000th of the liver (Sanai and Keeffe, 2010; Randazzo et al., 2012; Mumtaz et al., 2019; Ratziu et al., 2005) to improve patient understanding. Additionally, there is significant intra- and inter-observer variability in histological interpretation and steatohepatitis diagnosis, making the diagnostic conclusions unreliable (Davidson et al., 2020; Imajo et al., 2021). This information should be included in the DCD.**	Thank you for your comment, which the committee has considered. A statement has been added to section 3.1 of the diagnostics guidance document: "Perspectum stated that biopsies sample 1/50,000th of the liver. MRI-based testing can image the whole liver."
45	Perspectum Ltd	3.4	*"Ultrasound-based tests such as transient elastography and acoustic radiation force impulse elastography (ARFI) are typically done before liver biopsy is considered (see sections 2.2 to 2.4). However, these tests may not be suitable for some people."* **The wording "may" should be replaced with "are".** Transient elastography has high failure rates, especially in obese patients where tests are often not possible due to body habitus, and has wide indeterminate zones between threshold values for ruling out or ruling in the presence of advanced fibrosis (Lazo et al., 2008; McDonald et al., 2018; Newsome et al., 2018) even when performed alongside other blood tests such as ELF or FIB-4 (Boursier, Sanyal and Ratziu, 2020). Further studies, such as Karlas et al (2015), show that ARFI, TE and ELF perform poorly in bariatric patients and did not improve after weight loss. TE has also been shown to be affected by the presence of diabetes, hypertension, dyslipidaemia (and steatosis) with these risk factors	Thank you for your comment, which the committee has considered. The suggested change has been made to section 3.4.

DIAGNOSTICS ASSESSMENT PROGRAMME

MRI-based technologies for assessing non-alcoholic fatty liver disease
Diagnostics Consultation Document – Comments
Diagnostics Advisory Committee date: 28 September 2022

Comment number	Name and organisation	Section number	Comment	NICE response
			modifying results from the M and XL probes differently (Bazerbachi et al., 2020). This was previously included in the response to the DAR but has not been properly addressed to date.	

EAG Addendum 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

EAG Report: Addendum 2 16 September 2022

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135067

Completed 16 September 2022

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

The National Institute for Health and Care Excellence (NICE) has asked the External Assessment Group (EAG) to respond to Diagnostic Consultation Comments (DCD) (July 2022). This report (Addendum 2) contains the EAG responses to key points raised in the comments (Section 2) and, as requested by NICE, additional analyses relating to patients who refuse biopsy and for whom a confirmatory biopsy is not available are presented in Section 3.

2 EAG RESPONSES TO DIAGNOSTIC CONSULTATION COMMENTS

2.1 Clinical effectiveness evidence used to populate the model

Perspectum Ltd wondered why other technologies had received a favourable opinion in guidelines/DAP/MTEP based on similar/lower levels of evidence and requested justification for the discordant approach to assessment.

Perspectum Ltd also considered that data from the RADIcAL1 trial reflected clinical practice and that model results should have been generated using these data.

EAG response

The role of the EAG is to provide technical advice to NICE; the EAG does not make decisions. However, in this appraisal, results from the EAG population prevalence threshold analysis (EAG report, Section 6.2.14) showed that the sensitivity and specificity of LMS for any diagnostic test strategy could be 100% and the ICER per QALY gained would still be above £30,000. If sensitivity and specificity values were lower than those used in the EAG base case analysis, then this would **decrease** the cost effectiveness of LMS+biopsy versus biopsy only for any diagnostic test strategy (i.e., increase the size of the ICER per QALY gained).

RADIcAL1 trial sensitivity and specificity data (0.625 and 0.9 respectively) for patients with Advanced NASH (NAS≥4, ≥F2) were submitted by Perspectum Ltd during consultation on the DAR. These data were calculated using results from 18 patients. It is not known at which point in the pathway these patients were biopsied and/or if they had indeterminate results from previous fibrosis testing.

Table 1 Cost effectiveness results using RADIcAL1 trial data: LMS+biopsy versus biopsy only

Diagnostic test strategy	Additional cost of LMS	Change in QALYs compared to biopsy	ICER per QALY
Advanced NASH (NAS≥4, ≥F2)	£199,040	0.63	£317,104

EAG=External Assessment Group; F=stage of fibrosis; ICER=incremental cost effectiveness ratio; LMS=LiverMultiScan; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year

2.2 Biopsy complication rates

Perspectum Ltd queried the approach used by the EAG to cost biopsy-associated AEs, specifically how the value of £8.54 was derived.

EAG response

The value of £8.54 is not the cost per complication, it is the average cost of complication per patient biopsied, i.e., the total cost of treating all complications experienced by patients biopsied divided by the total number of patients biopsied. The average cost per complication can be calculated by dividing the average cost of complication per person biopsied (£8.54) by the risk of complication used in the EAG model (0.85%), leading to an average cost of £1005 per complication in the EAG base case.

Costs of death (or more accurately terminal care costs) have not been included in the model for three reasons:

1. the terminal care costs associated with biopsy are included in the costs of complications (i.e., any hospital stay due to the complication that caused the death)

2. as noted by the EAG and the company (RADIcAL1 trial summary results provided during the consultation period), death resulting from a biopsy is a rare event (1 in 10,000 [Thomaides-Brears 2021]). This means that even if the terminal care costs were significantly higher than just the complication costs considered in the model, the terminal care costs per person biopsied would be insignificant. For example, if the terminal care costs were £10,000, their addition to the model would only add £1 to the EAG estimated cost per biopsy of £814 (cost of procedure and complications)

3. if terminal care costs were included in the model, then they would also need to be added to the early deaths of people who had false negative LMS/MRE test results and those who had a delayed diagnosis. Early deaths due to a delayed diagnoses may outweigh the deaths due to biopsy; however, as the number of early deaths due to delayed diagnoses is unknown, the directional impact on the ICER per QALY gained of including terminal care costs cannot be determined.

In conclusion, the EAG considers that if the terminal care costs from death due to biopsy were included in the model, the impact on the cost effectiveness results would be insignificant.

The EAG has carried out LMS threshold analyses (Table 2). For the Advanced NASH (NAS≥4, F≥2) diagnostic test strategy, the results showed that the average cost per complication needs to increase from £1005 in the EAG base case to £102,631 to generate an ICER of £20,000 per QALY gained. In comparison, the (weighted average) cost of a gastrointestinal bleed is £3,232 (NHS Reference Costs HRG code: FD03A-FD03H). Results are also presented for the most cost effective diagnostic test strategy, Brunt Grade ≥2.

Table 2 Cost of complications: results from a threshold analysis

Diagnostic test strategy	Threshold: £20,000 per QALY			Threshold: £30,000 per QALY		
	Original complication cost*	Threshold cost	Increase from original	Original complication cost*	Threshold cost	Increase from original
Brunt Grade ≥2	£1,005	£86,834	8,640%	£1,005	£86,146	8,572%
Advanced NASH (NAS≥4, F≥2)**	£1,005	£102,631	10,212%	£1,005	£103,623	10,311%

* Cost of complications per person is £8.54
** South West quadrant (saving per QALY lost)
NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

2.3 Disutility values

1. Perspectum Ltd sought information on the origin and interpretation of the 0.03 disutility value used in the model. The company also wondered how a disutility of 0.03 could occur if the patients were asymptomatic
2. Perspectum Ltd questioned the rationale behind the disutility value that the EAG chose to use to represent the loss of utility associated with biopsy-related complications
3. Perspectum Ltd asked the EAG to provide in-depth calculations to allow a more thorough review of the disutility values used in the model and also to re-estimate disutility values.

EAG response to issue 1

The source of the 0.03 disutility is the NG49 Appendices (p610, Table 62). It is the difference between two utility values: NAFLD/NASH treated (0.87) and NAFLD/NASH untreated (0.84). The EAG carried out a comprehensive targeted search using appropriate key words (including, liver, utility, NAFLD, NASH, EQ-5D, and NICE). The best source of utility values that the EAG was able to find was NG49. The EAG recognises Perspectum Ltd's concern about the size of this disutility value; however, the EAG has carried out an analysis that showed that reducing the disutility associated with a delayed diagnosis to zero does not change the conclusions that can be drawn from EAG model results (See EAG Addendum 19 May, Table 4; all ICERs per QALY gained exceed £100,000).

The EAG considers that excluding the QALY loss associated with a false negative LMS test result cannot ever be a plausible scenario. If having a false negative LMS test result does not lead to a QALY loss, then there is no difference, in terms of QALYs, between a correct and an incorrect diagnosis. If this is the case, then there is no reason to perform a biopsy, or any of the other tests in the diagnostic pathway. The EAG considers that if patients are asymptomatic during the 6 months prior to having the second LMS test, the QALY loss should be interpreted as a loss in QALYs because of a delayed diagnosis. A delayed diagnosis means that the disease is more advanced at the time of diagnosis which could mean more severe symptoms and potentially reduced life expectancy. The EAG accepts the actual magnitude of the QALY loss associated with a delay in diagnosis of 6 months is unknown but considers that the assumption of no QALY loss would render the whole diagnostic pathway meaningless.

EAG response to issue 2

The EAG model is populated with the best clinical and economic evidence available. EAG analyses have demonstrated that the LMS+biopsy testing strategy reduces the number of unnecessary biopsies compared with the biopsy only strategy.

The EAG considers that the utility value associated with a biopsy complication used by Stevenson was extreme (utility decrement of 0.2, equivalent to 10 weeks of zero quality of life) and was biased against biopsy. As the most serious AE (death) was accounted for separately in the EAG model, the EAG considered that a more realistic assumption was to model 1 week with a zero quality of life to reflect the effect on utility of AEs not resulting in death. The EAG apologises that this was not made clear in the EAG report.

The EAG threshold analysis results (EAG original report, Section 6.2.14) showed that if LMS test results were 100% accurate, the ICERs for all the most cost effective strategy (Brunt Grade ≥2) would **ONLY** fall below £20,000 (£30,000) per QALY gained if the population prevalence was ≤39.7% (≤45.9%). Therefore, the population prevalence for all other diagnostic test strategies would need to be lower than 39.7% (45.9%).

The EAG has carried out LMS threshold analyses (Table 3). For the Advanced NASH (NAS≥4, F≥2) diagnostic test strategy, the results showed that the QALY loss associated with biopsy-related complications (0.000147) would need to increase by 29,252% (to 0.043) or by 19,728% (to 0.029) for LMS+biopsy to be cost effective versus biopsy only at thresholds of £20,000 per QALY and £30,000 per QALY, respectively. Results are also presented for the most cost effective diagnostic test strategy, Brunt Grade ≥2.

Table 3 Biopsy-related disutility value: results from a threshold analysis

Diagnostic test strategy	Threshold: £20,000 per QALY			Threshold: £30,000 per QALY		
	Original QALY loss	Threshold QALY loss	Increase from original	Original QALY loss	Threshold QALY loss	Increase from original
Brunt Grade ≥2	0.000147	0.037	25,170%	0.000147	0.024	16,327%
Advanced NASH (NAS≥4, F≥2)	0.000147	0.043	29,252%	0.00147	0.029	19,728%

NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

EAG response to issue 3

In-depth calculations are provided in Section 6.2.10 of the EAG report. This section of the EAG report has been reproduced below.

It has been reported that death directly related to percutaneous liver biopsy occurs in a maximum of 1 in 10,000 people biopsied (Thomaides-Brears 2021); this value has been used in the EAG model. In line with the population modelled in the Eddowes 2018 study, the EAG has assumed that the average age of patients who have a percutaneous liver biopsy is 54 years. Based on average life expectancy in the UK, patients aged 54 years are expected to live a further 32.5 years (ONS life expectancy calculator). However, patients with NAFLD have a lower than average life expectancy, living, on average, 6 years less (i.e., 26.5 years) than the general population (Shang 2021).

The age dependent utility value for someone aged 60 in the UK is 0.80. This means that the undiscounted total QALY loss for every biopsy related death is 21.2 (26.5x0.8=21.2). Discounted at an annual rate of 3.5% leads to a loss of 14.14 QALYs. Applying a probability of death of 1 in 10,000 people biopsied generates a QALY loss of 0.00141 per biopsy (14.14/10,000).

The EAG explored uncertainty by carrying out a threshold analysis to determine what the QALY losses associated with a biopsy would need to be for the most cost effective EAG base case diagnostic test strategy to become cost effective at thresholds of £20,000 and £30,000 per QALY gained. This analysis (original EAG report, Table 20) is reproduced in Table 4.

Table 4 QALY loss associated with biopsy: results from threshold analyses

Diagnostic test strategy	Threshold: £20,000 per QALY			Threshold: £30,000 per QALY		
	Original QALY loss	Threshold QALY loss	Increase from original	Original QALY loss	Threshold QALY loss	Increase from original
Brunt Grade ≥2	0.007	0.044	514%	0.007	0.031	340%
Advanced NASH (NAS≥4, F≥2)	0.007	0.050	701%	0.007	0.036	504%

NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

2.4 Lifestyle interventions

Perspectum Ltd wondered why NICE/EAG did not consider lifestyle intervention as a treatment for NAFLD/NASH (as it does with abstinence in alcoholic liver disease) despite its well proven effectiveness. The company considered that the model should be updated to incorporate this treatment option.

Perspectum Ltd considered that the EAG should have taken into account the evidence provided by McKay 2021 about people's understanding of NAFLD and/or their adherence to lifestyle advice or interventions.

EAG response

Advice to the EAG from a SCM is that, as part of standard hepatology practice, patients with indeterminate results from fibrosis testing and those with a confirmed diagnosis will be offered lifestyle advice relating to, for example, exercise, weight loss and alcohol use. Lifestyle advice will be provided irrespective of LMS/MRE results. Further, there is no quantitative evidence to demonstrate that the uptake of lifestyle advice (and hence the effectiveness of this advice) is higher following a diagnosis than prior to a diagnosis.

The EAG has performed threshold analyses (Table 5) to estimate the magnitude of the QALY gain that needs to be accrued through increased adherence to lifestyle advice (already provided) for the LMS+biopsy strategy to be cost effective. At thresholds of £20,000 and £30,000 per QALY gained, the QALY gain would need to be 0.013 and 0.009, respectively, for the Advanced NASH (NAS≥4, F≥2) diagnostic test strategy. Results are also presented for the most cost effective diagnostic test strategy, Brunt Grade ≥2.

Table 5 QALY gain associated with LMS-related lifestyle advice: results from a threshold analysis

Diagnostic test strategy	Threshold: £20,000 per QALY		Threshold: £30,000 per QALY	
	Original QALY gain	Threshold QALY gain	Original QALY gain	Threshold QALY gain
Brunt Grade ≥2	0	0.012	0	0.008
Advanced NASH (NAS≥4, F≥2)	0	0.013	0	0.009

NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

The EAG clinical impact review includes the McKay 2021 paper (original EAG report, Section 5.4). McKay 2021 provides qualitative evidence that LMS improves some patients' understanding of NAFLD. However, it does not provide any evidence of improved lifestyle compliance following a LMS test result.

2.5 Test failure rate

Perspectum Ltd considered that NICE/the EAG should explicitly comment on the high failure rates and availability of existing tests to provide context when discussing potential limitations of new diagnostic tools. The company stressed that, unlike ultrasound technologies and MRE, LMS was not confounded by body habitus.

Perspectum Ltd was concerned that published MRE failure rates had not been used in EAG scenario analyses.

EAG response

The EAG highlights that the available MRE evidence does not relate to the population specified in the final scope issued by NICE and, therefore, results should not be used to inform decision making (or to compare LMS+biopsy versus MRE+biopsy).

The MRE failure rate of 25% highlighted by Perspectum Ltd was reported in a study published in 2009, and more recent evidence shows lower failure rates. The EAG has carried out analyses using a failure rate of 15.3% (highlighted by Perspectum Ltd, DCC comment 11 [Wagner 2017]) and, in response to a request by NICE, this analysis has been carried out with and without an additional cost for MRE (MRI: £148.24; additional MRE cost: £59.50). Results are presented in Table 6 and Table 7, respectively, and do not change the conclusions that can be drawn from EAG MRE base case results.

Table 6 MRE results generated using a failure rate of 15.3% (additional cost of MRE added to the standard cost of MRI)

Diagnostic strategy	Additional MRE cost	Change in QALYs compared to biopsy only	ICER per QALY gained (MRE+biopsy vs biopsy only)	Increase in ICER compared to 5.5% failure rate in EAG base case
Any fibrosis (≥F1)	£173,182	-1.54	Dominated by straight to biopsy	Remains dominated
Significant fibrosis (≥F2)	£80,183	0.25	£314,454	£84,487
NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	£139,567	-0.87	Dominated by straight to biopsy	Remains dominated
Advanced NASH (NAS≥4, ≥F2)	£99,891	-0.30	Dominated by straight to biopsy	Remains dominated

EAG=External Assessment Group; F=stage of fibrosis; ICER=incremental cost effectiveness ratio; MRE=magnetic resonance imaging; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year

Table 7 MRE results generated using a failure rate of 15.3% (no additional cost of MRE to standard cost of MRI)

Diagnostic strategy	Additional MRE cost	Change in QALYs compared to biopsy only	ICER per QALY gained (MRE+biopsy vs biopsy only)	Increase in ICER compared to 5.5% failure rate in EAG base case
Any fibrosis (≥F1)	£97,923	-1.54	Dominated by straight to biopsy	Remains dominated
Significant fibrosis (≥F2)	£212	0.25	£830	No longer dominates
NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	£62,695	-0.87	Dominated by straight to biopsy	Remains dominated
Advanced NASH (NAS≥4, ≥F2)	£19,769	-0.30	Dominated by straight to biopsy	Remains dominated

EAG=External Assessment Group; F=stage of fibrosis; ICER=incremental cost effectiveness ratio; MRE=magnetic resonance imaging; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year

2.6 EAG apparent errors

Perspectum Ltd questioned the EAG estimate of the QALY decrement associated with biopsies (percutaneous biopsy and transjugular biopsy).

EAG response

The EAG was unable to identify any published evidence on the impact of biopsy complications on utility values. Where no data or evidence are available, it is standard health economic modelling practice to use assumptions which, where possible, are based on clinical opinion, to estimate parameter values. However, in this instance, clinicians were unable to provide any insight into the impact of biopsy-related complications on utility values.

As previously stated, the EAG considers that the utility value associated with a biopsy complication used by Stevenson was extreme (utility decrement of 0.2, equivalent to 10 weeks of zero quality of life) and was biased against biopsy. As the most serious AE (death) was accounted for separately in the EAG model, the EAG considered that a more realistic assumption was to model one week with a zero quality of life (i.e., a utility decrement of 0.02) to reflect the effect on utility of AEs not resulting in death. The EAG apologises that this was not made clear in the EAG report.

The EAG considers that the modified Stevenson assumption still generates a loss in QALYs associated with biopsy-related complications (excluding death) that is very high. In the recently published NICE appraisal of icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides (TA805), the disutility used to reflect the loss in utility associated with a serious bleed (i.e., a bleed requiring hospitalisation) was −0.104. The duration of this disutility was not reported; however, to achieve the EAG model QALY loss associated with biopsy-related complications that do not result in death (0.02, i.e., 1 week of zero HRQoL), the bleed-related disutility in TA805 would have to last for 67 days, i.e., (-0.104*67)/365=0.02.

For completeness, the EAG has also generated cost effectiveness results for LMS+biopsy versus biopsy only (Table 8) and MRE+biopsy versus biopsy only (Table 9) using the higher utility loss associated with biopsy-related complications suggested by the company (0.00147 compared to 0.000147 used in the EAG base case analysis).

Table 8 LMS+biopsy versus biopsy only: using an average QALY loss from biopsy complications of 0.00147

Diagnostic test strategy	Additional LMS cost	Change in QALYs compared to biopsy only	ICER per QALY gained	Change in ICER compared to EAG base case
Any fibrosis (≥F1)	£344,671	-0.85	Dominated by biopsy only	Remains dominated
Significant fibrosis (≥F2)	£310,655	-1.30	Dominated by biopsy only	Remains dominated
Advanced fibrosis (≥F3)	£260,617	0.14	£1,838,566	No longer dominated
Brunt Grade ≥1	£411,556	-2.78	Dominated by biopsy only	Remains dominated
Brunt Grade ≥2	£243,770	0.63	£388,444	-£878,067
NASH (NAS≥4, >=1 for lobular inflammation and hepatocyte ballooning)	£277,597	-0.35	Dominated by biopsy only	Remains dominated
Advanced NASH (NAS>4, >F2)	£260,684	0.14	£1,864,394	No longer dominated
High Risk (NASH or >F1) (Eddowes)	£394,320	-3.71	Dominated by biopsy only	Remains dominated

EAG=External Assessment Group; F=stage of fibrosis; ICER=incremental cost effectiveness ratio; LMS=LiverMultiScan; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year

Table 9 MRE+biopsy versus biopsy only: average QALY loss from biopsy complications of 0.00147 (additional cost for MRE [£59.50] added to the cost of an MRI)

Diagnostic test strategy	Additional MRE cost	Change in QALYs compared to biopsy only	ICER per QALY gained	Change in ICER compared to EAG base case
Any fibrosis (≥F1)	£169,184	-1.55	Dominated by biopsy only	Remains dominated
Significant fibrosis (≥F2)	£65,424	0.65	£101,337	-£128,630
NASH (NAS≥4, >=1 for lobular inflammation and hepatocyte ballooning)	£131,679	-0.74	Dominated by biopsy only	Remains dominated
Advanced NASH (NAS≥4, ≥F2)	£87,412	-0.01	Dominated by biopsy only	Remains dominated

EAG=External Assessment Group; F=stage of fibrosis; ICER=incremental cost effectiveness ratio; MRE=magnetic resonance imaging; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year

2.7 Updating the EAG report

The company queried why an update to the EAG report was not permitted during the DAR process (for example, why were data presented by Simon 2021 not added to the EAG report).

EAG response

The EAG highlights that the NICE SCMs have access to feedback from consultation and so will have been able to take into consideration the additional information provided by the company.

Simon 2021 (DCC comment 16) considers mortality in a biopsy-confirmed Swedish (nationwide) cohort with non-alcoholic fatty liver disease. The information provided in this study underscores the importance of reversing all stages of NAFLD and shows that all histological stages of NAFLD are associated with significant increased risk of overall mortality which increased with worsening NAFLD severity. This information is important and provides useful context, no matter the method of diagnosis.

2.8 Waiting times

Perspectum Ltd considered that the model should be revised to account for biopsy waiting time, for example by extending the time horizon. Perspectum Ltd also suggested that additional research on MRI waiting times should be performed and included in the model as a sensitivity analysis

EAG response

Faster diagnosis time was an outcome identified in the NICE scope. During the first DAC meeting, the committee considered that delays for MRI and biopsy are likely to vary by hospital trust. No data were identified to support running a scenario showing improved time to diagnosis relating to any of the interventions considered; nor was the EAG able to identify information on the effect of waiting times on patient outcomes, including disease progression.

2.9 Additional evidence

The company asked NICE/the EAG to consider using data from Imajo 2021, Jayaswal 2020, Pavlides 2017 in the EAG model.

EAG response

The EAG worked within the final scope issued by NICE and used the best available data. The cost effectiveness results presented in the EAG report were generated using LMS data relating to the population that are the focus of this appraisal, and results for MRE were

presented in Addendum 1 using results presented by Imajo 2021 (not the population of interest).

The Jayaswal 2020 paper was included in the EAG's clinical impact review. However, the paper only reported hazard ratios; diagnostic test accuracy (2x2) data, i.e., data that could be used in the EAG model, were not reported.

The Pavlides 2021 paper was included in the EAG's diagnostic test accuracy review. However, the paper did not include any diagnostic test accuracy data for the population of interest; information for the population of interest was available from the Eddowes publication.

The EAG reiterates that diagnostic accuracy could be 100% and LMS would still not generate ICERs less than £30,000 per QALY gained due to the high proportion of patients for whom advanced fibrosis cannot be ruled out and who therefore also need to be biopsied.

2.10 Re-conceptualisation of the model

The company requested that the model be reconceptualised in line with published literature within the disease space. The company considered that the 6-month model time horizon introduced two failings:

1. the impact of a 'false negative' on the QALYs gained. The report states a QALY loss of 0.03 'per year' which has no meaning within an analysis over 6-months
2. the QALY loss associated with early mortality. It is not clear how this value has been calculated but it is unfeasibly low and clearly does not account for QALYs lost beyond the first 6 or 12-months of the analysis period

EAG response

It is assumed in the EAG model that all patients are given a correct diagnosis at 6 months and there are no differences between arms in patient outcomes and costs after this point. This is an optimistic assumption. Extending the model time horizon would involve delaying the second scan until, say, 2 or 3 years after the first scan (rather than after 6 months), or assuming that the second scan was not 100% accurate. Employing these alternative assumptions would only increase the QALY loss associated with LMS/MRE false negative results and would therefore reduce the cost effectiveness of LMS/MRE (i.e., increase the ICER per QALY gained). Further, there is no quantitative evidence to demonstrate the negative effects (increased costs and QALY losses) that would be incurred due to a delayed diagnosis.

Responses to questions 1 and 2

1. In the model, the QALY loss associated with a false-negative (0.03 per annum) is applied for 6 months, i.e., 0.03/2=0.015.

2. The QALY loss from a biopsy-related death is not restricted to 6 months; it relates to the whole period of life lost and is applied as a one-time payoff.

   In the RADIcAL1 trial summary results provided during the consultation period, the company used Thomaides-Brears 2021 data to support the view that death resulting from a biopsy is a rare event (1 in 10,000). The QALY loss associated with death is substantial and has been estimated using assumptions that are likely to over-estimate the actual QALY loss given the ill health of the patients being biopsied.

2.11 Cost of MRE

Perspectum Ltd asked that the MRE cost estimate used in the model should comprise the cost of an MRI scan plus an additional cost and that a clearer distinction should be made between MRE and LMS.

EAG response

Results from the EAG analyses (EAG Addendum 1, Table 13, reproduced in Table 10) showed that MRE+biopsy (when compared with biopsy only) was not a cost effective option at thresholds of £20,000 and £30,000 per QALY gained when the cost of MRE was estimated using the cost of an MRI scan plus an addition cost of £59.50 for MRE (based on information provided by Resoundant), i.e., £207.74.

Table 10 MRE plus biopsy versus biopsy (1,000 patients) – total MRE cost at which MRE becomes cost effective at different WTP thresholds

Diagnostic test strategy		MRE cut-off score	Base case prevalence from CALM trial	£20,000/QALY	£30,000/QALY
				Total cost of MRE (i.e., MRE+MRI)	
T1	Any fibrosis (≥F1)	2.9kPa	87%	£50.70*	£37.48*
T2	Significant fibrosis (≥F2)	3.3kPa	65%	£164.58	£166.63
T6	NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	3.3kPa	54%	£93.70*	£86.35*
T7	Advanced NASH (NAS≥4 plus ≥F2)	3.5kPa	48%	£139.80*	£137.34*

*South West quadrant (saving per QALY lost)
F=stage of fibrosis; MRE=magnetic resonance elastography; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year; WTP=willingness to pay

2.12 Using LMS/MRE results to inform patient management

Perspectum Ltd highlighted that, in line with a patient expert comment, they considered that a positive LMS was sufficient to inform patient management.

Resoundant considered that the NICE scope should have focused on MRI-based technologies that can replace liver biopsy.

EAG response

The EAG asked NICE Specialist Committee Members the following question:

> *Based on currently available diagnostic test accuracy data, would you be satisfied that LMS (or MRE) can replace biopsy for patients with indeterminate or discordant TE results? Please elaborate (patients/circumstances/etc).*

The responses are presented in Box 1.

Box 1 Specialist Committee Members responses

I do not think that either test currently can reliably replace biopsy as neither has been tested in large or randomised trials. The sensitivity and specificity of LMS in particular is not high enough to replace biopsy. MRE seems more promising but more work is needed to answer clinical questions such as this LMS (and MRE) might be useful in assessing and monitoring fibrosis stage but I doubt it would replace the need for liver biopsy completely. Even in advanced NASH biopsy is likely to remain important in the assessment of important disease co-factors (alcohol, iron, autoimmune disease)

The EAG highlights the following text from the NICE Diagnostic Consultation Document (Section 3.10):

> *Clinical experts commented that current data on test performance was not sufficient to be confident in a diagnosis without a biopsy. So, they would refer people with positive MRI [-based technology] test results for a liver biopsy. But if further data provides reassurance on test accuracy, a follow-up biopsy may not always be needed.*

In summary, clinical advice was that the diagnostic test accuracy data currently available was not strong enough for LMS/MRE to replace biopsy in clinical practice. In response to a request from NICE, the EAG has run a hypothetical scenario which generates results for the comparison of LMS/MRE only versus biopsy only (Section 3.3).

2.13 Model populated with unreliable data

Perspectum Ltd emphasised their view that many model assumptions and inputs were not reliable and was concerned that guidelines were being developed based on results from analyses that used these unreliable inputs. Perspectum Ltd were also concerned that the EAG did not complete a probabilistic sensitivity analysis.

EAG response

The EAG model is populated with the best clinical and economic data available. Clinical assumptions used in the model have been validated by clinical experts. Results from threshold analyses showed that parameter values would need to be many magnitudes different to change the conclusions that can be drawn from EAG base case results.

The EAG model is a single node decision tree and, therefore, is linear by design. Thus, exploring the impact of non-linearity by undertaking probabilistic sensitivity analyses is not relevant. Probabilistic sensitivity analyses will not strengthen weak evidence or validate model assumptions.

The NICE lead team requested that non-linearity was confirmed through increasing and decreasing model parameters by ±20%, averaging the incremental cost effectiveness ratios (ICERs per QALY gained) from these analyses and comparing them with the deterministic base case ICERs per QALY gained. The EAG performed this analysis. The results (EAG Addendum 1, Table 1) showed that, depending on the test strategy, the difference between the ICERs per QALY gained generated from averaging results from the ±20% analyses and the deterministic ICERs per QALY gained was between 0.01% and 0.02%.

The analysis shows that even if the EAG is wrong about the structural linearity of the model, the analyses performed show that any impact of non-linearity is not important for decision making.

2.14 Availability of biopsy paired data

Perspectum Ltd raised concern that all available biopsy paired data had not been considered by the NICE Committee.

EAG response

In line with the final scope issued by NICE, the EAG considers that only 266 unique biopsy-paired patient datapoints are eligible for inclusion in the review. The EAG's reasons for excluding the studies suggested by Perspectum Ltd are presented in Table 11.

The EAG was unable to appraise all of the pre-specified thresholds from the Andersson study (≥800ms, ≥825ms, ≥875ms, ≥900ms and ≥925ms) because data were only available for the ≥800ms and ≥875ms thresholds.

As diagnostic test accuracy data were available for the population of interest, the EAG did not consider it appropriate to use data from other populations in the EAG economic analyses presented in the original EAG report. Following a request from NICE, the EAG has used

diagnostic test accuracy data from the RADIcAL1 trial (not clear whether these data have been collected from the population described in the final scope) to generate cost effectiveness results (Table 1). The EAG reiterates that, in the population of interest, even if LMS were 100% accurate then if would not be cost effective at current prices because of the population prevalence.

Table 11 EAG reasons for exclusion of studies highlighted by the company*

Publication	Patient conditions	Biopsy paired	Unique biopsy paired	Reason for exclusion
Banerjee, R., et al. (2014)	VH, NASH, ArLD, PSC/PBS	~~79~~	~~0~~	According to the corresponding author, the Pavlides 2017 study population included the Banerjee 2014 study population and therefore the EAG does not regard the studies as two independent data sets
Eddowes, P., et al. (2017)	VH, NASH, ArLD, PSC/PBS	50	0	Included
Pavlides, M., et al. (2017)	NAFLD	71	0	Included
McDonald, N., et al. (2018)	VH, NASH, ArLD, PSC/PBS	~~142~~	~~142~~	The McDonald study population included the Eddowes study population and therefore the EAG does not regard the studies as two independent data sets. It was not possible to distinguish between the patients included in the Eddowes study and other patients
Harrison, S.A. et al. (2019)	NAFLD	~~43~~	~~43~~	The Harrison study included the wrong patient population. Patients in the Harrison study had a liver biopsy confirmed histological diagnosis at entry into the study which included staging of fibrosis. The final scope issued by NICE defined the population of interest as patients for whom advanced fibrosis or cirrhosis has not yet been diagnosed
Levick C., et al. (2019)	NAFLD, VH, ArLD	~~19~~	~~0~~	The Levick study assessed portal hypertension which was not an outcome of interest defined in the final scope issued by NICE
Jayaswal et al. (2020)	NAFLD, VH, ArLD	~~178~~	~~178~~	The Jayaswal study was included in the clinical impact review because the study assessed the prognostic ability of the LiverMultiScan cT1 output to predict clinical outcomes for a population that included patients with NAFLD for whom advanced fibrosis or cirrhosis had not been diagnosed (n=85/197). However, the Jayaswal study did not assess or report diagnostic test accuracy (2x2) data
Dennis et al. (2020)	NAFLD	~~86~~	~~0~~	The Dennis study included patients with biopsy-confirmed NAFLD (wrong patient population). Furthermore, the Dennis study included the Eddowes study population and therefore the EAG does not regard the studies as two independent data sets
Janowski et al., (2020)	AIH	~~60~~	~~0~~	The Janowski study included patients with autoimmune hepatitis (not the focus of this appraisal)
Mole et al. (2020)	Cancer	~~128~~	~~128~~	The Mole study included patients who underwent liver resection for cancer (not the focus of this appraisal)
Amerikanou et al., (2021)	NAFLD	~~98~~	~~98~~	Patients in the Amerikanou study did not undergo liver biopsy. There were no comparative data for LiverMultiScan versus liver biopsy

Dennis et al. (2021)	NAFLD	~~264~~	~~0~~	The Dennis study did not report any outcomes of interest and included the Eddowes and the Pavlides study populations. Therefore, the EAG does not regard the studies as independent data sets
Imajo et al., (2021)	NAFLD	145	0	Included
Harrison et al., (2021)	NAFLD	~~260~~	~~260~~	The population had not received previous tests for fibrosis (study population not the focus of this appraisal). LiverMultiScan and FibroScan were used to determine the prevalence of NAFLD and NASH in a cohort of asymptomatic middle-aged Americans
Beyer et al., (2021)	NAFLD	~~581~~	~~581~~	Only data from study 2 of the Beyer study were eligible for inclusion. However, the study 2 data included the Imajo 2021 study population and therefore the EAG does not regard the studies as two independent data sets
Janowski et al., (2021)	AIH/ASC	~~66~~	~~66~~	The Janowski study included patients with autoimmune hepatitis and patients with autoimmune sclerosing cholangitis (not the focus of this appraisal)
Andersson et al., (2021)	NAFLD	~~543~~	~~26~~	The Andersson study is a meta-analysis of data from five studies: the Pavlides study (included, EAG report, Section 5.3), Imajo study (included, EAG report, Section 5.3), McDonald study (included data from the Eddowes study that could not be separated from Eddowes data; see above); Harrison study (see reason for exclusion above) and the Siddiqui study (available as an abstract only). Therefore, the EAG does not regard the studies as independent data sets
Total		266	0	

* Where data are struck through, the EAG did not consider that the data were relevant for inclusion

AIH=autoimmune hepatitis; ArLD=alcohol-related liver disease; ASC=autoimmune sclerosing cholangitis; EAG=External Assessment Group; NAFLD=non-alcoholic fatty liver disease; NASH=non-alcoholic steatohepatitis; PBS=primary biliary cholangitis; PSC=primary sclerosing cholangitis; VH=vascular hepatopathy

2.15 Uncertainty around the care of patients with NAFLD

Perspectum Ltd raised concern that the model did not consider:

1. clinical care across fibrosis stages and that the proportion of physicians performing biopsies varied across the world
2. geographical inequalities with existing tests
3. lifestyle interventions.

EAG response

1. the focus of the EAG model is on NHS practice and, therefore, modelling variations in practice across the world is not appropriate
2. geographical inequalities could not be accounted for in the model due to a lack of diagnostic test accuracy (2x2) data to explain how local testing pathways vary across the NHS
3. lifestyle advice has been discussed in Section 2.4.

3 EXPLORATORY ANALYSES: NO CONFIRMATORY BIOPSY

3.1 Introduction

There is no evidence on clinical outcomes for using LMS/MRE in place of a biopsy, or for patients who refuse a biopsy. The EAG highlights the following text from the NICE Diagnostic Consultation Document (Section 3.10):

> *Clinical experts commented that current data on test performance was not sufficient to be confident in a diagnosis without a biopsy. So, they would refer people with positive MRI [-based technology] test results for a liver biopsy. But if further data provides reassurance on test accuracy, a follow-up biopsy may not always be needed.*

However, in response to comments from Resoundant (DCC comment 38) and NICE, the EAG has run two exploratory scenarios:

- LMS/MRE (no confirmatory biopsy) versus no biopsy (i.e., for patients who refuse a biopsy) (Section 3.2)
- LMS/MRE (no confirmatory biopsy) versus biopsy only (Section 3.3).

3.2 EAG exploratory analyses: LMS/MRE (no confirmatory biopsy) versus no biopsy

If LMS/MRE were used without a confirmatory biopsy, then the consequences for an individual with a **false positive** result could be:

(i) a QALY loss due to the anxiety of being told that their liver disease is more advanced than it actually is

(ii) costs and QALY losses from treating a stage of liver disease that they do not have

(iii) a QALY loss from failing to treat the state of liver disease that the patient actually has

(iv) no QALY benefits associated with the clinical information obtained from biopsies (for example, help determine the extent of liver damage, help predict prognosis, and inform future treatment decisions).

(v) no QALY loss or costs associated with biopsy

(vi) A change in costs and QALYs associated with any change in monitoring of patients following an LMS/MRE diagnosis.

The values of these costs and QALY losses are not known, although given that the treatment options for patients who do not have advanced fibrosis are essentially lifestyle advice, which has already been delivered to these patients, the costs and QALY losses associated with treatment of patients with false positive results are likely to be limited.

For patients with **true negative** LMS/MRE results, there are no cost or QALY benefits arising from preventing an unnecessary biopsy as the patient was never going to have had a biopsy. The patient may experience some benefit arising from a reduction in anxiety due to having been told that their liver disease was less severe than they had feared.

The implications of **true positive** LMS/MRE results (or **false negative** LMS/MRE results for patients who have true positive results following a second LMS) for patients who refuse to have a biopsy are complex. For example, patients who have a LMS test cT1 score >875ms could receive a diagnosis of NASH or Advanced NASH (NAS≥4, F≥2); however, according to data presented by Eddowes, these patients are highly likely to have advanced fibrosis (≥F3). If these patients are only diagnosed with NASH (despite also having fibrosis), or Advanced NASH (despite actually having advanced fibrosis) then these patients will have received incomplete diagnoses (although they will all have true positive results in the sense that they have NASH or Advanced NASH). Similarly, if MRE were used to diagnose advanced fibrosis, then patients who are correctly diagnosed with advanced fibrosis and refuse to have a biopsy may actually have cirrhosis; the cirrhosis diagnosis may be delayed and/or missed until the patient presents with cirrhosis-related symptoms.

For the no biopsy strategy, clinical advice to the EAG is that currently patients with indeterminate results from fibrosis testing who refuse biopsy will have yearly check-ups and repeat fibrosis testing at 3 or 5 years. These patients will not incur the cost of a biopsy, but the severity of their liver disease will remain undiagnosed until their disease becomes symptomatic or severity is confirmed by future fibrosis testing. There is no evidence that can be used to robustly model the costs and benefits of this diagnostic pathway.

Clinical advice to the EAG is that patients who are at high risk of cirrhosis and refuse a biopsy will be monitored via 6 monthly appointments with ultrasound and blood testing for hepatocellular carcinoma surveillance. It is, therefore, possible that, for patients who refuse a biopsy, the availability of LMS/MRE could result in more frequent monitoring if the patient's LMS/MRE test result indicates a high risk of cirrhosis (however determined). The clinical utility of more frequent monitoring in the population of interest who refuse a biopsy is not known.

Due to the uncertainties relating to QALY gains and losses associated with strategies that do not include a biopsy, the EAG has not been able to generate QALYs; however, for these strategies, test outcomes, number of tests and cost of tests can be calculated using the EAG base case model. Therefore, the EAG has undertaken exploratory threshold analyses (Section 3.2.1 and Section 3.2.2) that identify the QALY gain per person that would need to be

generated to justify using an LMS/MRE (no confirmatory biopsy) strategy versus a no biopsy strategy (effectively the current position for patients who refuse a biopsy).

Due to the uncertainties about the impact of failed tests when there is no confirmatory biopsy, failed tests were not considered in the EAG analyses. The EAG has retained the base case assumption that all patients with a negative initial LMS/MRE test result will have a second LMS/MRE which is assumed to result in a correct diagnosis. As the model is only estimating the cost of LMS/MRE, the timing of the second LMS/MRE test is not relevant.

3.2.1 LMS (no confirmatory biopsy) versus no biopsy

For 1,000 patients refusing biopsy and receiving LMS, using a cut-off of 875ms to diagnose NASH or Advanced NASH, and using Eddowes diagnostic test accuracy data (EAG base case), of the 1,000 initial LMS tests, there will be 500 patients with negative test results who will have a follow up LMS at 6 months. This gives a total cost of testing for the LMS strategy of £520.86 per patient. The total cost of the no biopsy strategy over 6 months is £0 per patient. The patient outcomes are as follows:

- 48% of all patients, irrespective of strategy, have undiagnosed advanced fibrosis (F≥3)
- the no biopsy strategy leads to 54% of patients having undiagnosed NASH, 48% having undiagnosed Advanced Nash and 83% undiagnosed as being at high risk (NASH or F>1)
- the LMS (no confirmatory biopsy) strategy, depending on how the 875ms cut off is interpreted, leads to false positive diagnoses (i.e., over-diagnoses) for: 21.8% of the 696 patients diagnosed with NASH, 29.1% of the 674 patients diagnosed with Advanced NASH, and 2.6% of the 484 patients diagnosed as being high risk. For full details see Table 12

To generate an ICER of £20,000 per QALY gained, the LMS (no confirmatory biopsy) strategy would need to generate 0.026 QALYs per patient more than the no biopsy strategy. To generate an ICER of £30,000 per QALY gained, the LMS (no confirmatory biopsy) strategy would need to generate 0.017 QALYs per patient more than the no biopsy strategy. The potential sources of any additional QALY gains are discussed on p21.

3.2.2 MRE (no confirmatory biopsy) versus no biopsy

For 1,000 patients refusing biopsy and receiving MRE, using a cut-off of 3.3kPa to diagnose significant fibrosis (F≥2), and using the diagnostic test accuracy data from Imajo 2021 (used in the EAG analyses presented in Addendum 1), of the 1,000 initial MRE tests, there will be

406 patients with negative results who will have a follow up MRE at 6 months. This gives a total cost of testing for the MRE strategy of £208.43 per patient (£292.08 per patient if an additional cost for MRE is added to the cost of an MRI). The total cost of the no biopsy strategy over 6 months is £0 per patient. The patient outcomes are as follows:

- 48% of all patients, irrespective of strategy, will have undiagnosed advanced fibrosis (F≥3). Although the company has a test threshold to diagnose advanced fibrosis, no test accuracy data relating to this threshold were available for the population of interest
- the no biopsy testing strategy will lead to 87% of patients having undiagnosed fibrosis (F≥1) and 65% of patients having undiagnosed significant fibrosis (F≥2)
- the MRE (no confirmatory biopsy) strategy will lead to false positive diagnoses for 8.3% of the 711 patients with significant fibrosis (F≥2). For full details see Table 13

To generate an ICER of £20,000 per QALY gained, the MRE (no confirmatory biopsy) strategy would need to generate 0.015 QALYs per patient more than the no biopsy strategy (0.010 per patient if MRE does not cost more than MRI). To generate an ICER of £30,000 per QALY gained, the MRE (no confirmatory biopsy) strategy would need to generate 0.010 QALYs per patient more than the no biopsy strategy (0.007 if MRE does not cost more than MRI).

Table 12 Proportion of patients diagnosed using the LMS (no confirmatory biopsy) strategy

Stage of condition	cT1 cut-off value	True positive (per 1000 successful tests)	True negative (per 1000 successful tests)	False positive (per 1000 successful tests)	False negative (per 1000 successful tests)	Total true positive after 2nd LMS	Total positives after 2nd LMS	Patients over-diagnosed
NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	875ms	348	304	152	196	544	696	21.8%
Advanced NASH (NAS≥4, ≥F2)	875ms	304	326	196	174	478	674	29.1%
High Risk (NASH or >F1) (Eddowes)	875ms	478	152	22	348	826	848	2.6%

F=stage of fibrosis; LMS=LiverMultiScan; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitisr

Table 13 Proportion of patients diagnosed using the MRE (no confirmatory biopsy) strategy

Stage of condition	Cut-off value	True positive (per 1000 successful tests)	True negative (per 1000 successful tests)	False positive (per 1000 successful tests)	False negative (per 1000 successful tests)	Total true positive after 2nd MRE	Total positives after 2nd MRE	Patients over-diagnosed
Significant Fibrosis (≥F2)	3.3kPa	535	289	59	117	652	711	8.3%

F=stage of fibrosis; MRE=magnetic resonance elastography; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitisr

3.2.3 LMS/MRE (no confirmatory biopsy) versus no biopsy: EAG concluding remarks

There is no available evidence on the effect of incorrect, under- or over-diagnosis on lost QALYs and unnecessary treatment/monitoring costs for diagnoses reached using an LMS/MRE (no confirmatory biopsy) strategy. While there may be QALY gains for patients with an accurate LMS/MRE test result who do not have a confirmatory biopsy, there is no evidence of the magnitude of this QALY gain. The difference in QALYs between the LMS/MRE (no confirmatory biopsy) strategy and the no biopsy strategy cannot be determined. Ultimately, if clinicians are not confident that a LMS/MRE test result is accurate, then they will not develop patient care plans based on LMS/MRE results. As such and given the lack of clinical evidence to properly inform the analyses, the EAG considers that these results should not be used to inform decisions.

3.3 LMS/MRE (no confirmatory biopsy) versus biopsy only

The EAG highlights that this comparison means that confirmatory biopsies are not carried out after positive LMS/MRE test results. The reduction in biopsies with this strategy is therefore 100%. For the same reasons outlined at the end of Section 3.2.3, the EAG considers that these results should not be used to inform decisions.

3.3.1 Model assumptions and costs

The QALY and cost assumptions relating to different test outcomes (true positive, true negative, false positive, false negative) used in the LMS/MRE (no confirmatory biopsy) strategy are the same as those described in Section 3.2. The assumptions used in the biopsy only strategy are those used in the EAG base case biopsy only strategy.

The unit costs for both strategies are the same as those described in the EAG report.

3.3.2 Cost effectiveness results

Cost effectiveness results for the comparison of LMS/MRE (no confirmatory biopsy) versus biopsy only are presented in Table 14, Table 15 and Table 16. These analyses differ from the EAG base case analyses which considered the comparison of LMS/MRE+biopsy versus biopsy only.

Table 14 Cost effectiveness results: LMS (no confirmatory biopsy) versus biopsy only per 1,000 patients

Diagnostic test strategy	Cost of LMS (no confirmatory biopsy)	Cost of biopsy only	Additional cost with LMS (no confirmatory biopsy) versus biopsy only	QALYs lost LMS (no confirmatory biopsy)	QALYs lost biopsy only	Additional QALYs with LMS (no confirmatory biopsy) versus biopsy only	Biopsies averted with LMS (no confirmatory biopsy) versus biopsy only	ICER per QALY
Any fibrosis (≥F1)	£411,556	£813,540	-£401,984	1.55	7.14	5.59	1,000	LMS (no confirmatory biopsy) dominates
Significant fibrosis (≥F2)	£511,311	£813,540	-£302,229	3.39	7.14	3.75	1,000	LMS (no confirmatory biopsy) dominates
Advanced fibrosis (≥F3)	£511,311	£813,540	-£302,229	2.47	7.14	4.67	1,000	LMS (no confirmatory biopsy) dominates
Brunt Grade ≥1	£411,556	£813,540	-£401,984	2.78	7.14	4.36	1,000	LMS (no confirmatory biopsy) dominates
Brunt Grade ≥2	£511,311	£813,540	-£302,229	2.15	7.14	4.98	1,000	LMS (no confirmatory biopsy) dominates
NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	£511,311	£813,540	-£302,229	2.78	7.14	4.36	1,000	LMS (no confirmatory biopsy) dominates
Advanced NASH (NAS≥4, ≥F2)	£511,311	£813,540	-£302,229	2.47	7.14	4.67	1,000	LMS (no confirmatory biopsy) dominates
High Risk (NASH or >F1) (Eddowes)	£511,311	£813,540	-£302,229	4.93	7.14	2.21	1,000	LMS (no confirmatory biopsy) dominates

EAG=External Assessment Group; F=stage of fibrosis; ICER=incremental cost effectiveness ratio; LMS=LiverMultiScan; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year

Table 15 Cost effectiveness results: MRE (no confirmatory biopsy) versus biopsy only per 1,000 patients (additional cost of MRE added to the standard cost of MRI)

Diagnostic test strategy	Cost of MRE (no confirmatory biopsy)	Cost of biopsy only	Additional cost with MRE (no confirmatory biopsy) versus biopsy only	QALYs lost MRE (no confirmatory biopsy)	QALYs lost biopsy only	Additional QALYs with MRE (no confirmatory biopsy) versus biopsy only	Biopsies averted with MRE (no confirmatory biopsy) versus biopsy only	ICER per QALY
Any fibrosis (≥F1)	£269,127	£813,540	-£544,413	2.59	7.14	4.55	1,000	MRE (no confirmatory biopsy) dominates
Significant fibrosis (≥F2)	£287,483	£813,540	-£526,057	1.66	7.14	5.47	1,000	MRE (no confirmatory biopsy) dominates
NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	£275,413	£813,540	-£538,127	2.24	7.14	4.90	1,000	MRE (no confirmatory biopsy) dominates
Advanced NASH (NAS≥4, ≥F2)	£288,068	£813,540	-£525,472	2.10	7.14	5.04	1,000	MRE (no confirmatory biopsy) dominates

EAG=External Assessment Group; F=stage of fibrosis; ICER=incremental cost effectiveness ratio; LMS=LiverMultiScan; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year

Table 16 Cost effectiveness results: MRE (no confirmatory biopsy) versus biopsy only per 1,000 patients (no additional cost of MRE added to the standard cost of MRI)

Diagnostic test strategy	Cost of MRE (no confirmatory biopsy)	Cost of biopsy only	Additional cost with MRE (no confirmatory biopsy) versus biopsy only	QALYs lost MRE (no confirmatory biopsy)	QALYs lost biopsy only	Additional QALYs with MRE (no confirmatory biopsy) versus biopsy only	Biopsies averted with MRE (no confirmatory biopsy) versus biopsy only	ICER per QALY
Any fibrosis (≥F1)	£192,045	£813,540	-£621,495	2.59	7.14	4.55	1,000	MRE (no confirmatory biopsy) dominates
Significant fibrosis (≥F2)	£205,143	£813,540	-£608,397	1.66	7.14	5.47	1,000	MRE (no confirmatory biopsy) dominates
NASH (NAS≥4, ≥1 for lobular inflammation and hepatocyte ballooning)	£196,531	£813,540	-£617,009	2.24	7.14	4.90	1,000	MRE (no confirmatory biopsy) dominates
Advanced NASH (NAS≥4, ≥F2)	£205,561	£813,540	-£607,979	2.10	7.14	5.04	1,000	MRE (no confirmatory biopsy) dominates

EAG=External Assessment Group; F=stage of fibrosis; ICER=incremental cost effectiveness ratio; MRE=magnetic resonance imaging; NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; QALY=quality adjusted life year

EAG report: Erratum 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

External Assessment Group report

Erratum 2

This report was commissioned by the NIHR Systematic Reviews Programme as project number 135067

Completed 10 October 2022

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Correction to Addendum 2, Table 3

In Addendum 2, Table 3, one of the original QALY loss values had been incorrectly input as 0.00147 instead of 0.000147. A corrected version of Table 3 is provided below.

Table 1 Biopsy-related disutility value: results from a threshold analysis

Diagnostic test strategy	Threshold: £20,000 per QALY			Threshold: £30,000 per QALY		
	Original QALY loss	Threshold QALY loss	Increase from original	Original QALY loss	Threshold QALY loss	Increase from original
Brunt Grade ≥2	0.000147	0.037	25,170%	0.000147	0.024	16,327%
Advanced NASH (NAS≥4, F≥2)	0.000147	0.043	29,252%	0.000147	0.029	19,728%

NAS=non-alcoholic fatty liver disease (NAFLD) activity score; NASH=non-alcoholic steatohepatitis; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

DIAGNOSTICS ASSESSMENT PROGRAMME

MRI-based technologies for assessing non-alcoholic fatty liver disease

EAG Addendum document – Comments

	Comment number	Section number	Comment
Resoundant	1	General	Overall, we thank the DAG and EAR for their work on this important issue. Of note, we thank the Programme for the iterative process and ability to provide feedback.
Resoundant	2	General	In general, we feel it's important to note that MRE is a distinct biomarker from LMS. They assess different physiological parameters and are at different stages of validations as a technology (MRE was cleared in the US in 2009 while LMS 2017). MRE is listed in multiple international clinical guidelines for use routine clinical use. In our view, these technologies should be considered separately.
Resoundant	3	Section 3.14, Page 16	"Test accuracy data for MRE is needed in the scope population" Unfortunately, we still have significant concerns about the scope of this review and believe it unnecessarily omits a large body of evidence in support for MRE. The scope requires that study populations only include those patients who had a failed ELF or Fibroscan™. However, it's not clear why this would be a required study population, as a failed ELF or Fibroscan™ exam has no bearing on the diagnostic capacity of a subsequent test such as MRE. There may be phenotypic factors of this population (tend to have higher BMIs, etc.) that may be of interest. However, this was not stated. However, if true, these sub-studies often exist and could be referenced by the Committee (e.g., diagnostic performance of MRE in patients with BMI >30). Adhering to this requirement limits the evidence which can be submitted and ultimately delays the implementation of mature, non-invasive biomarkers that are currently being used in health systems all around the world.
Resoundant	4	Section 3.10, Page 13	"The EAG's model assumed that all people with a positive result from MRI testing would then be referred for a confirmatory biopsy." According to both NG49 (NAFLD Assessment and Management, July 2016) and MIB216 (Fibroscan™ for assessing liver fibrosis and cirrhosis, June 2020), a positive score (above the stated threshold for each technology) both non-invasive technologies was deemed sufficient to rule-in advanced liver disease without needed a confirmatory biopsy. This was done even though it's been well-published that both ELF and

	Comment number	Section number	Comment
			Fibroscan™ suffer from poor positive predictive value (PPV). Under these guidance documents and technology reviews, the amount of over-treatment and risk of drug-induced liver injury (when pharmacotherapies are available) could be unacceptably high. While this is certainly concerning in its own right, it also makes the methodology in this Diagnostic Assessment appear counterintuitive and discordant (i.e., any positive MRI biomarker must have a confirmatory biopsy 100% of the time). In nearly all meta analyses, MRE has been shown to be superior in both PPV/NPV and sensitivity/specificity. In short, it does not seem to make sense that a less accurate technology (e.g., ELF, Fibroscan™) would not require confirmatory biopsy, while the more accurate technology (MRE) must require a confirmatory biopsy.
Resoundant	5	Section 3.7, Page 12	"No data for MRE was identified specifically in the scope population, or at specified cut-off values for advanced fibrosis or cirrhosis" We must emphasize that **Resoundant does not have stated manufacturer cut offs.** It is stated in the assessment by the DAG, but we are not sure from where this statement originated. On our website, we maintain a blog post of suggested *range of cut offs* for corresponding fibrosis stages that are used at our parent institution, Mayo Clinic, and can be used by other institutions depending on their goal (maximize AUROC, maximize PPV/NPV, etc). These are thresholds used by one institution and are not company-determined cut offs. As such, they should not be the only thresholds evaluated. Rather, as was done with ELF and Fibroscan™, we recommend the DAG assess the significant body of literature and determine which cut offs for MRE best support the intended use (high NPV to rule out the need for subsequent biopsy, etc). For example, in DG50 (cirrhosis over 16 years old), NICE Guidelines identify a range of possible VCTE cut offs based on the significant literature: "Data relating to transient elastography was reported at a range of thresholds: low (9-to <13 kPa), medium (13 to <15kPa), high (≥15 kPa)." In looking at ways to evaluate AUROC, DG50 summarizes potential results: . The following criteria were used for evaluating AUCs: • ≤0.50: worse than chance • 0.50–0.60: very poor • 0.61–0.70: poor • 0.71–0.80: moderate • 0.81–0.92: good • 0.91–1.00: excellent or perfect test.

	Comment number	Section number	Comment
			We note that across all stages of fibrosis (F1-F4), multiple meta analyses (pooled or Individual Participant Data) show that MRE has a “good” or “excellent or perfect test” against paired biopsy according the NICE criteria for diagnostic accuracy.
Resoundant	6	Section 3.2, Page 22	“For patients with true negative LMS/MRE results, there are no cost or QALY benefits arising from preventing an unnecessary biopsy as the patient was never going to have had a biopsy.” We disagree with this conclusion. As BMI is a confounding factor for Fibroscan™, it’s likely that a patient with an elevated BMI (e.g., >30) would have repeat failed Fibroscan™ exams. It is also likely that at some point, the clinician would become unsatisfied with the lingering non-diagnosis and refer for liver biopsy. It should be noted that most patients at risk for NAFLD and NASH match this phenotype (elevated BMI). Therefore, having a second line of noninvasive testing that works well in patients with high BMI would be welcome prior to biopsy. Therefore, a True Negative result from MRE (prior to that biopsy) would thus obviate the need for biopsy in a large number of patients who are expected to have indeterminate or technical failures with Fibroscan™. Those QALY savings appear real and quantifiable.
Resoundant	7	Section 3.13, Page 15	“The EAG’s model included costs of doing MRI, but not any costs for changes to NHS infrastructure that may be needed for more MRI use.” Issue: Adding £52 to the cost of MRE to account for the capital costs of adding more MRE capacity. While we understand the need to account for capital costs associated with adding new technologies, we’re concerned with the consistency of the methodology here. Firstly, in looking once again at previous guidance (DG50) for adding VCTE (Fibroscan™) to the clinical workflow, there was no economic model that we found where the capital costs of adding new Fibroscan™ devices was taking into consideration. Of note, the Fibroscan™ devices are often more expensive than adding MRE to an existing MRI scanner. Therefore, it seems inconsistent with previous guidance and economic modelling to include these costs, particularly on a per scan basis (as was done for MRE). Also of note, LiverMultiScan also requires a propriety pulse sequence (e.g., MyoMaps, CardiaQuant, Proton-density fat fraction, IDEAL/IQ, Liver Labs) to be added to the scanner, which can often cost £20,000-£40,000+. This added capital cost was no included in the model for adding LiverMultiScan either. Finally, the model that was employed seems flawed: a.) it underestimates the number of patients who will likely need MRE, and b.) it does not take into account that when an aging UK scanner is due to be replaced, the cost for MRE when purchasing a new MRI scanner is typically £0. In terms of a. (underestimating the number of

	Comment number	Section number	Comment
			patients), the model used by the EAG assumes that the population needing fibrosis assessment will stay the same over the next 10 years. This is contrary to every study projecting the rise of NAFLD and NASH in the U.K., which show exponential growth over the coming decade. While we realize that the EAG notes that this rough model is built on many uncertainties, this appears to be an evidence-based adjustment which would bring down the projected capital costs of adding MRE tremendously. Lastly, for b. (real cost of MRE could be £0 if MRE is simply added to new scanner purchases), the EAG should emphasize that the true costs of adding MRE capacity would approach £0 if the U.K. were to prioritize the inclusion of MRE (at £0) to the scheduled replacement of outdated MRI scanners moving forward.
Resoundant	8	General	Issue: low cost MRE. MRE exams uses significantly less MRI scanner time and resources than a typical abdominal MRI. To reflect this lower use of resources, US payers have adopted a lower payment code (CPT code 76391) for standalone MRE. This represents a -40% discount from the full abdominal MRI cost in the U.S. If the NICE and the U.K. system were to take a similar approach, this -40% discount on the current reimbursement for an abdominal MRI (£149) would instead be £89.40. We would encourage both the EAG and NICE to consider a pathway where low-cost, standalone MRE was implemented to reflect the lower resource utilization of MRE exams. No evidence is required for the EAR to consider this option and make a recommendation for implementation should it be deemed appropriate.
Perspectum Ltd	1		For ease of review, we have grouped our responses into the following three sections 1. Previous comments from Perspectum that were ignored during the DCD commenting period 2. Factual inaccuracies within the addendum 2 (updated analysis) 3. Further comments in response to the Addendum 2
	Previous comments from Perspectum that were ignored during the DCD commenting period		
Perspectum Ltd	2	Throughout	During initial DCD consultation, Perspectum raised many comments that have not been addressed in the addendum 2 (new analysis). Note: Comment numbers are those from the DCD commenting table (14th July 2022).

	Comment number	Section number	Comment
			Comment 4: The DCD needs to include management guidelines for CCGs that do not have access to tests such as TE or ELF. This can further raise the issue of health inequalities or patient care being reliant on geographical area. **How will NICE guidelines manage this lack of access given the NHS long term plan to advance equality and reduce health care inequalities?** It is disappointing to see NICE effectively ignoring underserved patient populations that would massively benefit from a comprehensive non-invasive diagnostic assessment that is currently unavailable. It is even more disappointing and indeed worrying to see care-giving clinicians ignore this striking set of statistics. At the very least, Liver*MultiScan* should be recommended where there are no ELF or TE tests available, in line with recommendations that all patients should have access to a non-invasive option. **Perspectum requests that the above comments ignored in the previous review (14th July 2022) are properly addressed either in another addendum or during the committee meeting so that all stakeholders have the necessary information to make informed decisions in this important guideline.**
Perspectum Ltd	3	Throughout	Comment 5 (see comment 2 above): How does NICE/EAG justify ignoring published literature and real-world evidence from UK clinical experts highlighting gaps in, and barriers to implementing existing NICE guidelines? These issues highlight the need for alternate and accessible non-invasive tests.
Perspectum Ltd	4	Throughout	Comment 9: The committee acknowledged that LiverMultiScan may be relevant in the care of a child, despite not being the population presented in the model as performing a biopsy on children is considered unsustainable. Perspectum feel this should be acknowledged in the public facing reports. Could we also get clearer justification on why performing a biopsy on an adult is more sustainable than on a child?
Perspectum Ltd	5	Throughout	Comment 10 (See comment 1 above): This update to the analysis [i.e., geographical variation in access to tests] would materially impact the results and ensure it is reflective and supportive of current practice and availability across NHS trusts, rather than an 'idealised' trust with all recommended tests available.
Perspectum Ltd	6	Throughout	Comments 12: The DCD should be more transparent regarding the issues with biopsy. For example, the sampling error (1/50,000th of the liver, Sanai and Keeffe, 2010; Randazzo et al., 2012; Mumtaz et al., 2019; Ratziu et al., 2005) should be included to help improve patient and clinician understanding. Additionally, there is significant intra- and inter-observer variability in

	Comment number	Section number	Comment
			histological interpretation and steatohepatitis diagnosis and staging, making the diagnostic conclusions unreliable (Davidson et al., 2020; Imajo et al., 2021). **This information should be included in the DCD.**
Perspectum Ltd	7	Throughout	Comment 18: Throughout the assessment, the issue of MRI capacity has been raised however not appropriately researched. No data or evidence was provided by the committee or EAG in the scale of potential impact; therefore, additional research should be performed and included in the analysis. Information regarding MRI usage for liver disease investigation and biopsy occurrence has been collected by Perspectum through Freedom of Information Requests and it is expected that the same information can be obtained by the EAG.
Perspectum Ltd	8	Throughout	Comment 29: (See comment 7 above) Given the absence of data presented to the committee to evidence this claim, Perspectum have submitted FOI requests to UK trusts to obtain real world data on MRI scan use over the past 5 years. Has the EAG/NICE made attempts to obtain this information as well?
Perspectum Ltd	9	Throughout	In addition, it is clear from patient testimonials (McKay et al., 2021) that biopsy is a painful and invasive procedure that patients would rather avoid: • "*Biopsy was very stressful and very painful. (The MRI) was a walk in the park in comparison to that"* • *"It felt exactly like you had been stabbed, which basically I suppose you have been"* • *"Because it was non-invasive. It doesn't cause me any problems. It's quick, it doesn't affect anything. Whereas with the alternative, a liver biopsy would be completely the opposite"* • *"I had two biopsies. I had one in 2011 and one in 2014. It's excruciatingly painful… And then you go back home, and this pain comes there for a number of days to heal up. Then that alone itself – the second time felt like I was going to have a panic attack… The drama that goes with a liver biopsy. They are separating you like an operation – it's traumatic. You know they make you feel as if they are going to chop you up. I wouldn't want to go through any liver biopsy again."*
	Factual inaccuracies		

<table>
<tr><th></th><th>Comment number</th><th>Section number</th><th>Comment</th></tr>
<tr><td>Perspectum Ltd</td><td>10</td><td>2 EAG responses to diagnostic consultation comments</td><td>Perspectum thanks the EAG for written responses to the consultation comments; however, we would like to ask why changes to model parameters have not been combined and the cost-effectiveness re-investigated. In sections, 2.2, 2.3, 2.4, 2.6, and 2.10, threshold analysis has been done and the increase in parameters needed to achieve cost-effectiveness is reported; however, any threshold analysis which modifies an input (such as a disutility) whilst holding other erroneous parameters constant is likely to be highly misleading.

Internal modelling, guided by an external independent health economist with expertise in diagnostics, has ascertained the following results based on corrections of the model parameters.

<table>
<tr><th>Input name</th><th>EAG model value</th><th>New model value</th><th>Justification</th></tr>
<tr><td>QALY loss: Biopsy complication</td><td>0.000147</td><td>0.00147</td><td>See comment 15</td></tr>
<tr><td>QALY loss: False negative</td><td>0.015</td><td>0.00</td><td>See comment 14</td></tr>
<tr><td>Cost: Biopsy complication</td><td>£8.54</td><td>£168.67 (Bajre et al., 2022)</td><td>This cost is taken from the Bajre paper. If complication rates taken from the Thomaides-Brears 2021 paper, and cost of major bleeding from Bajre 2022, the expected cost would be higher than this.</td></tr>
<tr><td>Cost: Second LMS for those with a TN & FN</td><td>£347.24</td><td>£0 – Perspectum has offered to pay for the 6 month scan for both TN & FN groups</td><td>Perspectum are willing to discuss this more with the EAG/committee/NICE team</td></tr>
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<tr><th></th><th>Comment number</th><th>Section number</th><th>Comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th></th><th>Total cost</th><th>Total QALY loss</th><th>Total cost</th><th>Total QALY loss</th><th>Difference in cost</th><th>Difference in QALYs</th><th>ICER/QALY gained with LMS</th></tr>
<tr><td>Any fibrosis (>=F1)</td><td>£1,240.860</td><td>0.00776</td><td>£974</td><td>0.00846</td><td>£267</td><td>0.001</td><td>£384,148</td></tr>
<tr><td>Significant Fibrosis (>=F2)</td><td>£1,080.760</td><td>0.00637</td><td>£974</td><td>0.00846</td><td>£107</td><td>0.002</td><td>£51,322</td></tr>
<tr><td>Advanced Fibrosis (>=F3)</td><td>£1,021.100</td><td>0.00586</td><td>£974</td><td>0.00846</td><td>£47</td><td>0.003</td><td>£18,208</td></tr>
<tr><td>Brunt Grade >=1</td><td>£1,320.910</td><td>0.00846</td><td>£974</td><td>0.00846</td><td>£347</td><td>0.000</td><td>--</td></tr>
<tr><td>Brunt Grade >=2</td><td>£1,000.710</td><td>0.00568</td><td>£974</td><td>0.00846</td><td>£27</td><td>0.003</td><td>£9,719</td></tr>
<tr><td>NASH (NAS>=4, >=1)</td><td>£1,041.190</td><td>0.00603</td><td>£974</td><td>0.00846</td><td>£68</td><td>0.002</td><td>£27,783</td></tr>
<tr><td>Advanced NASH (NAS>=4, >=F2)</td><td>£1,020.950</td><td>0.00585</td><td>£974</td><td>0.00846</td><td>£47</td><td>0.003</td><td>£18,141</td></tr>
<tr><td>High Risk (NASH or >F1) (Eddowes)</td><td>£1,222.460</td><td>0.00760</td><td>£974</td><td>0.00846</td><td>£249</td><td>0.001</td><td>£290,832</td></tr>
</table>

Perspectum request that the model is either re-estimated using appropriate inputs, the model re-conceptualised in line with published health economic literature (See comment 27 of initial DCD review (14th July 2022)) or these results are presented to the Diagnostic Advisory Committee.
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<tr><th></th><th>Comment number</th><th>Section number</th><th>Comment</th></tr>
<tr><td>Perspectum Ltd</td><td>11</td><td>2.2 Biopsy complication rates</td><td>
We thank the EAG for providing some clarity on how the average cost of complication per person biopsied was calculated. Our substantive query was why did the EAG not update (i.e., inflate or improve the estimate) the assumption used within the Stevenson et al. (2012) for the average cost of a complication of £1000. The £1,000 from the Stevenson (2012) was a hypothetical value which bears little resemblance to the costs today of treating/managing a major complication associated with liver biopsy. Given preventing unnecessary biopsies and associated biopsy complications, in the form of costs and consequences, is the primary value proposition for LiverMultiScan, a fair characterisation of the negative impacts of biopsy is necessary to show any potential for value.

The recent Bajre et al. (2022) publication, led by the Oxford Academic Health Sciences Network (who drive the adoption and spread of innovative ideas and technologies across large populations), utilised NHS tariffs to present an average cost of £4,592.50 for major bleeding as a result of liver biopsy complication. The EAG's own analysis on page 5 reported a value of £3,232 highlighting that complication costs are in fact far higher than the original assumed cost of £1,000.

Based on Bajre et al. 2022 and the EAG's own analysis, £1,000 is a substantial underestimate of the complications associated with a biopsy, please see table below.

<table>
<tr><th>Original average cost of biopsy complication</th><th>Alternative value</th><th>Percentage increase</th></tr>
<tr><td>£1000</td><td>£4,592.50 (Bajre et al., 2022)</td><td>359.25%</td></tr>
<tr><td>£1000</td><td>£3,232 (EAG addendum 2, page 5)</td><td>223.20%</td></tr>
</table>

Furthermore, we cannot validate the £8.54 exactly because it is unclear how the EAG has inflated the value used in the Stevenson paper. However, if we take the figure of £1,000 from a ten-year-old paper, and inflate it, it is unclear how this could only come to £1,005.
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<tr><th></th><th>Comment number</th><th>Section number</th><th>Comment</th></tr>
<tr><td></td><td></td><td></td><td>Note, the updated ICER analysis presented in comment number 10 uses the lower bound per patient healthcare management cost of liver biopsy related complications.

Perspectum request that either the model is re-estimated, with appropriate base-case assumptions or the assessment is handed to an alternative EAG.</td></tr>
<tr><td>Perspectum Ltd</td><td>12</td><td>2.2 Biopsy complication rates</td><td>“The risk of complication used in the EAG model (0.85%)”

Perspectum would like to acknowledge that the probability of death resulting from a biopsy has been taken from the recent Thomaides-Brears et al., 2021 publication (1 in 10,000); however, we would like the EAG to update the risk of biopsy complications from 0.85% to the corresponding value from the Thomaides-Brears paper. The following complication rates are presented in the paper:

<table>
<tr><th>Complication type</th><th>Incidence rate</th></tr>
<tr><td>Major complication</td><td>2.44%</td></tr>
<tr><td>Major bleeding</td><td>0.48%</td></tr>
<tr><td>Moderate/severe pain</td><td>0.34%</td></tr>
<tr><td>Minor complication</td><td>9.53%</td></tr>
<tr><td>Pain</td><td>12.9%</td></tr>
<tr><td>Technical failure</td><td>0.91%</td></tr>
</table>

Perspectum request that the analysis be updated with variables from a consistent and up to date source and highlight the increased risk of complication that can arise from a liver biopsy. This should be included in all public facing documents to increase patient understanding and awareness.</td></tr>
<tr><td>Perspectum Ltd</td><td>13</td><td>2.3 Disutility values</td><td>Table 3: Biopsy-related disutility value: results from a threshold analysis

There is a likely typo within the table (copied below with queried figures highlighted) which should be addressed. Given that this figure has been disputed (Section 2.6), there needs not only to be a clarification regarding these values, but extra attention to detail given, especially when reporting results.</td></tr>
</table>

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<tr><th></th><th>Comment number</th><th>Section number</th><th>Comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th rowspan="2">Diagnostic test strategy</th><th colspan="3">Threshold: £20,000 per QALY</th><th colspan="3">Threshold: £30,000 per QALY</th></tr>
<tr><th>Original QALY loss</th><th>Threshold QALY loss</th><th>Increase from original</th><th>Original QALY loss</th><th>Threshold QALY loss</th><th>Increase from original</th></tr>
<tr><td>Brunt Grade ≥2</td><td>0.000147</td><td>0.037</td><td>25,170%</td><td>0.000147</td><td>0.024</td><td>16,327%</td></tr>
<tr><td>Advanced NASH (NAS≥4, F≥2)</td><td>0.000147</td><td>0.043</td><td>29,252%</td><td>0.00147</td><td>0.029</td><td>19,728%</td></tr>
</table>

Perspectum request that this is corrected within the analysis. Unfortunately, this lack of detail places doubt on the EAG's capability and we request that the model is either re-conceptualised or handed to an alternative EAG.
</td></tr>
<tr><td>Perspectum Ltd</td><td>14</td><td>2.3 Disutility values</td><td>Regarding the EAG response to issue 1

We thank the EAG for clarifying where they sourced the one year 0.03 disutility value from and for acknowledging the concern around the size of this disutility value. Now it is established this value has been derived from 2 health states reported on NG49, we highlight the NG49 summary of utility values:

"2 out of the 9 utility values were based on authors' assumptions. The remaining utilities were derived from other causes of chronic liver disease than NAFLD/NASH. [NG49 Appendices, page 441]"

The EAG implicitly recognise this and so to rationalise its use of the large disutility, they acknowledge that they force an interpretation on this disutility value that is separate to its actual purpose within the 6-month model. The forced interpretation is that unknown and unquantified QALY losses will occur in the future beyond the 6-months as a result of delayed diagnosis, not because of any disutility during the 6-month period. The mechanism to properly reveal any potential QALY losses cannot be captured in the EAG analysis and has not been modelled. By contrast, the economic modelling in NG49 characterised the natural history of this NAFLD/NASH population in an appropriate model structure over a suitable time horizon.</td></tr>
</table>

	Comment number	Section number	Comment
			We note again, that the EAG approach does not follow the NICE (2022) manual for how effectiveness and cost-effectiveness can be established over an appropriate time horizon. Neither does it follow approaches used in the literature to model this disease. Therefore, little confidence can come from the EAG's analysis. It is also worth noting that the cohorts used for the NG49 and DAP59 analysis are different (45 years in NG49 and 60 years in DAP59). Given the age dependence of disutility values and their prominence in the EAG's analysis, the high uncertainty in these disutility values is of particular concern. Perspectum also note that NG49 is scheduled to be reviewed and/or updated in the coming months. How do we ensure that the outcomes of DAP59 are aligned with NG49 which could potentially be updated? **Perspectum request, that given the compounding errors within the analysis and lack of justification from the EAG, that the assessment is either re-estimated, or handed to an alternative EAG.**
Perspectum Ltd	15	2.3 Disutility values	*Regarding the EAG response to issue 2* We thank the EAG for clarifying the discrepancy between the utilities used within the model and the methods for how these were calculated, in the original DAR. However, after it is now clarified, we are concerned that the Stevenson et al., (2012) assumed disutility that the EAG considered extreme has now been replaced by a disutility 10 times smaller. Clearly for an intervention that seeks to minimise disutility associated with invasive biopsies, and associated complications, it is important to be as accurate as possible regarding this potential value. We note in the addendum a typo/conflation between the 0.00147 (as implied by Stevenson et al) and 0.000147 (as assumed by the EAG). We note that the QALY loss associated with adverse events associated with a biopsy is a function both of the disutility size and frequency. The overall net-benefit loss is a function of the QALY loss and the cost of treating those adverse events (which in turn is based on a

	Comment number	Section number	Comment
			frequency). Consequently, any threshold analysis which modifies an input (such as a disutility) whilst holding other erroneous parameters constant is likely to be highly misleading. **Perspectum request that the model is either re-estimated using appropriate inputs, the model re-conceptualised in line with published health economic literature (See comment 27 of initial DCD review (14th July 2022)) or results from comment 10 are presented to the Diagnostic Advisory Committee.**
Perspectum Ltd	16	2.6 EAG apparent errors	*"The EAG was unable to identify any published evidence on the impact of biopsy complications on utility values"* We thank the EAG for acknowledging that they did not report the method to calculate disutilities associated with complications correctly in the original report. Whilst this reporting error is understandable given the limited reporting approach used to describe the model, we are concerned about the implications for the wider validity of the analysis. As previously discussed, the original Stevenson (2012) assumption for the disutility associated with complications was ten times higher than the EAG assumption which was not derived using clinical input. Therefore, we question how this value can be viewed as reasonable. Moreover, the wider consequences, for this input but for many others, are that the analysis has been reported with insufficient transparency to check the validity of the work. As an example, the disutility of a false negative is a function of a series of calculations including health state utilities but each step to calculate the end models' 'input' was not included either in the write-up or in the shared model. This is unsatisfactory and seriously undermines the transparency and reproducibility of the evaluation. The approach adopted by the EAG of changing one parameter input at a time, holding all else the same, does not reflect the uncertainty in the inputs and mitigate for potential errors in the inputs as well as those inputs to be unreasonable assumptions. **Perspectum request that either the model is re-estimated, with appropriate base-case assumptions or the assessment is handed to an alternative EAG.**

	Comment number	Section number	Comment
Perspectum Ltd	17	2.10 Re-conceptualisation of the model	*"The company requested that the model be re-conceptualised in line with published literature within the disease space."* We note the EAG have not commented upon why they chose to conceptualise the model differently to the previous NICE guidance for this disease, as well as most frequently used approaches in the literature. We do not understand why the EAG does not follow the NICE Manual / reference case and adopt a model and an associated time horizon which is appropriate for the decision-problem. We have not suggested a re-conceptualisation to show a more or less cost-effective technology but rather to ascertain quantitatively the impact of avoiding biopsies on the overall benefits and harms to patients and cost-effectiveness to the health care system and how this compares to diagnosis through a liver biopsy. The EAG speculates how cost-effectiveness would be affected with changes to the time horizon or incorporating the underlying natural history of the disease but rather than speculate or assert, we would prefer that these scenarios were modelled. We note the EAG response when they say: *"Further, there is no quantitative evidence to demonstrate the negative effects (increased costs and QALY losses) that would be incurred due to a delayed diagnosis."* We would suggest that the point of such a model is to generate such values, given reasonable assumptions on the natural history of the disease and the impact on length of life, quality of life and costs from a delayed diagnosis. Set against that are the costs of biopsies, complications, the frequency of adverse events and associated disutilities. An alternative conceptualisation would have allowed these various trade-offs to be explored without recourse to strong assumptions, such as a 0.03 disutility for a delayed diagnosis of an asymptomatic disease-period over 6-months. We note the EAG states that the QALY-loss for complications is taken over a lifetime: *"The QALY loss from a biopsy-related death is not restricted to 6 months; it relates to the whole period of life lost and is applied as a one-time payoff."*

	Comment number	Section number	Comment
			But we note that the model time horizon is clearly stated as being 6-months in the original report (Table 14 EAG base case model assumptions). We agree the appropriate model horizon should be a lifetime, as the EAG implicitly implies also, but we are concerned about the premise of starting with a short-term horizon but then selectively choosing elements to consider over a lifetime. Again, the inconsistency in approach and reporting means we have limited confidence in the validity of the results and analysis. **Perspectum request that either the model is re-estimated, with appropriate base-case assumptions or the assessment is handed to an alternative EAG.**
Perspectum Ltd	18	2.11 Cost of MRE	*"Results from the EAG analyses (EAG Addendum 1, Table 13, reproduced in Table 10) showed that MRE+biopsy (when compared with biopsy only) was not a cost-effective option at thresholds of £20,000 and £30,000 per QALY gained when the cost of MRE was estimated using the cost of an MRI scan plus additional cost of £59.50 for MRE".* We would like to thank the EAG for clarifying this information, however, would like to question the methods and costs associated with the additional cost of MRE (£59.50). Based on the analysis in EAG Addendum 1, Perspectum would like to highlight the following things: 1. "*Resoundant Inc provided information to the EAG that the approximate cost of adding MRE to an existing MRI scanner would be in the region of £35,000".* a. Resoundant's own website advertises a sample acquisition cost of over $100,000 (£84,000, https://www.resoundant.com/radiology). **Perspectum request that a breakdown of the MRE cost £35,000 is provided and why it is not consistent with publicly available information.** 2. *"The number of MRI machines in the UK was estimated in 2017 to be 6.1 per million population.* a. Perspectum would like to query why an updated value was not used when the following are publicly available: 1) https://www.statista.com/statistics/473302/number-of-magnetic-resonance-

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			imaging-units-united-kingdom-uk/ showing that in 2014, the number of MRI units in the UK was 467; 2) https://data.oecd.org/healthcat/magnetic-resonance-imaging-mri-units.htm showing that the number of MRI machines within the UK is higher than previously anticipated. **Perspectum request that the analysis updated using appropriate data or provide justification as to why the above sources are not appropriate.** 3. "*Applying this to the population of England suggested that there were approximately 345 MRI machines in England in 2017"* **a.** Perspectum would like to query why the number of MRI scanners used to calculate this cost are for the **UK** (England, Scotland, Wales and Northern Ireland), whereas the population of **England** was used in the cost calculation. **Perspectum request that this analysis is updated with consistent geographical variables.** 4. "*The cost of adapting 34 MRI machines"* *a.* Perspectum would like to query the impact of only upgrading 10% of MRI machines within the UK/England (see point 3). One of the NHS's long term goals is to reduce geographical inequalities, however if only 10% of MRI machines were upgraded, this introduces greater inequalities, especially for those with indeterminate fibrosis testing, and in those regions with a lower density of MRI scanners. Not only will these patients feel let down by already existing tests, but they would be reliant on being within a reasonable travelling distance to one of these 34 scanners. **Perspectum would like the EAG to justify hampering patients from receiving appropriate care and re-estimate a realistic cost of performing MRE within this patient population.**
Perspectum Ltd	19	2.15 Uncertainty around the care of patients with NAFLD	*"The focus of the EAG is on NHS practice and, therefore, modelling variations in practice across the world is not appropriate. Geographical inequalities could not be accounted for in the model due to the lack of diagnostic test accuracy (2x2) data to explain how local testing pathways vary across the NHS."* Perspectum feel that these two comments contradict one another. The focus cannot be on the NHS only without addressing the differences in practice within the NHS. The geographical inequalities highlighted previously are within the NHS. If the analysis is applied to an 'ideal'

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			trust, then it increases geographical inequalities within the UK, hampering the care provided to a large proportion of the UK and failing to address NHS long terms goals. Furthermore, there is no rationale for believing diagnostic test accuracy is dependent on the region within the UK in which the test is performed. **Perspectum request that the analysis is either redone to account for these differences in care or more data is collected regarding this, and the guidelines publication is paused until this can be addressed.**
Perspectum Ltd	20	2.12 Using LMS/MRE to inform patient management	*"LMS (and MRE) might be useful in assessing and monitoring fibrosis stage but I doubt it would replace the need for liver biopsy completely. Even in advanced NASH biopsy is likely to remain important in the assessment of important disease co-factors (alcohol, iron, autoimmune disease)."* Perspectum thanks the EAG for reaching out to the specialist committee members for their opinion. Respectfully, that opinion is outdated. For certain diagnoses, such as autoimmune hepatitis, a biopsy is necessary, but even then, monitoring can be done cost-effectively with Liver*MultiScan* (Bajre et al., 2022). For the assessment of iron overload, biopsy is no longer indicated and only recommended to assess liver damage secondary to haemochromatosis (Wood et al., 2005, Garbowski et al., 2014). For steatohepatitis, imaging outperforms biopsy in sampling, accuracy and predicting adverse clinical outcomes (Imajo et al., 2021). **Perspectum request that evidence pertaining to AIH and, iron and alcohol related issues be considered by the EAG and committee members – especially as they have been raised as conditions impacting clinician decision making within the NAFLD/NASH disease space.**
	Further comments in response to the Addendum 2		
Perspectum Ltd	21	2.3 Utility values	Regarding EAG response to issue 3 We thank the EAG for clarifying how the utility of a biopsy death was calculated which was missing from the original report. We inferred that a death related to a QALY loss of approximately 0.5 of a quality adjusted year, given the time horizon of the model of 6-months.

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			We are unsure about long-term QALY losses given the stated time-horizon of the model being 6-months.For more information, please see comments 13, 14, and 15. We agree with the use of the Thomaides-Brears 2022 paper for probability of death and agree the QALY loss, given a lifetime horizon, is likely to be similar to the value calculated by the EAG. We note however, that the EAG assumes a utility of 0.80 at death (age-adjusted for a 60-year old population) but recall figures of 0.87 and 0.84 being used for the utility values of individuals with treated disease and untreated disease (PH53). Again, we suggest there is tremendous uncertainty in any of the utility values used within this analysis which casts significant doubt on its validity. The significant issues with the EAG's approach to mitigating for this uncertainty, in which they perform a threshold analysis on a given input independent from all other inputs, has been commented in previously in comment 10 and 15. **Perspectum request that either the model is re-estimated, with appropriate base-case assumptions or the assessment is handed to an alternative EAG.**
Perspectum Ltd	22	2.8 Waiting times	*"Nor was the EAG able to identify information on the effect of waiting times on patient outcomes, including disease progression."* The NICE committee members (rather than EAG) should also be considering patient and public satisfaction as paramount importance when making decisions on these clinical guidelines, as highlighted by the lay member in this NICE committee who previously presented comments regarding patient preference and satisfaction. The most recent British Social Attitudes (BSA) survey (2021) reports the main reason that people gave for being dissatisfied with the NHS overall was waiting times for GP and hospital appointments (65 per cent). In addition, there is an increasing trend in public dissatisfaction regarding waiting times; the percentage of people citing waiting times as a reason for satisfaction saw and 11 percentage point decrease compared to 2019 (https://www.kingsfund.org.uk/publications/public-satisfaction-nhs-social-care-2021). Perspectum has performed a Freedom of Information analysis in addition to a review of publicly available sources (See FOI Summary 26Sep2022). This analysis has revealed a

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			waiting time for consultation in gastroenterology ranging from 19 to 38 weeks, and can therefore be longer than the 6 month time horizon used in the EAG's analysis. Introducing Liver*MultiScan* would advocate for improved patient experience and satisfaction by reducing the number of unnecessary liver biopsies and hence the number of patients experiencing long liver biopsy wait lists. **Perspectum request that the impact of waiting times for gastroenterology is not only considered by the EAG, but also by the committee members, when considering the impact of introducing non-invasive technologies with the potential to reduce the demand on gastroenterology services.**
Perspectum Ltd	23	2.15 Uncertainty around the care of patients with NAFLD	*"The focus of the EAG is on NHS practice and, therefore, modelling variations in practice across the world is not appropriate"* From experience, Perspectum has found that payers across the world and other governing bodies will look to NICE guidance for advice on new technologies and the evidence produced in these assessments, therefore thinks that the EAG should not be limited to UK practice only. In addition, the comment that this response is written for provided the following publication: 'An international survey on patterns of practice in NAFLD and expectations for therapies – The POP-NEXT project'. Perspectum would like to highlight that whilst this publication investigates the differences between countries in NAFLD patient care pathways and management across the world, this paper highlights findings **from the UK**, however, these UK findings have not been considered. In addition, this paper highlights biopsy refusal which has not been accounted within the model. Rather than assuming 100% of the population would refuse a biopsy (Section 3.2.1), Perspectum request that the EAG model a scenario in which 25% of the population refuse a liver biopsy. More information on biopsy refusal can be found in the FOI Summary.
Perspectum Ltd	24	2.15 Uncertainty around the care of patients with NAFLD	"*Geographical inequalities could not be accounted for the in the model due to the lack of diagnostic test accuracy (2x2) data to explain how local testing pathways vary across the NHS"*

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			Perspectum would like to query the efforts made to obtain this information, especially as information was provided to NICE by Perspectum that highlighted the differences across NHS trusts. Information from East and North Hertfordshire NHS Trust, West Hertfordshire Hospitals NHS Trust and Homerton University Hospital NHS Foundation Trust (City and Hackney Clinical Commissioning Group) however been ignored by the EAG and committee.
Perspectum Ltd	25	2.9 Additional evidence	*"The Jayaswal 2020 paper was included in the EAG's clinical impact review. However, the paper only reported hazard ratios; diagnostic test accuracy (2x2) data, i.e., data that could be used in the EAG model, were not reported"* 2x2 tables for prognostic test accuracy for event-free survival and all-cause mortality were included in Table S19 within the supplementary information. This cohort included a significant proportion of NAFLD/NASH patients and proves that the fixation on tying non-invasive biomarkers of liver disease severity solely to an invasive liver fibrosis measurement taken from within a 50,000th of liver is unnecessary and outdated. The gold standard against which non-invasive biomarkers should be measured is patient outcomes, not liver biopsy, an imperfect 'gold standard' measure of pathology, whose staging is not based on linear increases in quantity of fibrosis, but on architectural changes as well (Please see comment 6 for more information).This is reflected by the US FDA's preference that in NASH clinical trials, liver fibrosis as measured by liver biopsy is only a surrogate endpoint to assist with accelerated approval, not a gold standard, and that efficacy of response to treatment should also be confirmed by significant improvements in patient outcomes. **Will the committee acknowledge that there are serious issues with attempting to tie novel biomarkers of liver disease to histology and that prediction of clinical outcomes and prognostic ability should be given more weighting?**
Perspectum Ltd	26	2.12 Using LMS/MRE to inform patient management	Primum non Nocere (first, do no harm) is a key principle of healthcare. One that is ignored when patients with asymptomatic disease are given a liver biopsy, especially when liver biopsy has a published complication rate of approximately 10%.

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			Compared to liver biopsy, scanning people is relatively benign. Time is taken up but there is no harm to the patient. When liver biopsy was introduced to assess NASH in the 1980s, there were no better or more benign alternatives. However, because biopsy is NOT benign, most doctors who see patients with NASH choose not to biopsy them, but to treat in the absence of a biopsy-confirmed diagnosis, because they do not want to harm their patient. This is especially poignant when one half of liver biopsies for suspected NASH in the UK show only minimal disease RADIcAL 1 data - these patients have been harmed for no benefit. The original scope of this NICE evaluation was to address the diagnostic needs of the ~3 million UK adults with NASH, who are at higher risk of liver and cardiac outcomes (Roca-Fernandez, 2022). In 2022, the evidence and patient experience (McKay et al 2022) clearly favours scanning as the less harmful way to diagnose not just an individual, but at a community or national level. The Special committee members may disagree on the utility of scanning, but they must acknowledge that biopsies are harmful, and thereby there is an ethical imperative to avoid them when we can. The committee has also discussed the risk of false negatives in patients who have LiverMultiScan. Patients with normal scans have no increased risk of clinical outcomes. Increased cT1, liver fat and increased liver iron content are all risk factors for disease - mpMRI determines all three, like a biopsy, but without the harm. A recent study of post-covid patients has highlighted a prevalence of liver injury of 28%. Would the committee advise all 28% of post-covid patients are biopsied? **Will this committee acknowledge the harm and risk done by liver biopsies, and acknowledge *Primum non Nocere*?**

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Perspectum Ltd	27	2.12 Using LMS/MRE to inform patient management	*"The sensitivity and specificity of LMS in particular is not high enough to replace biopsy."* The committee has also advised that the diagnostic test accuracy was not strong enough, however, the Jayaswal (2020) paper showed that LiverMultiScan was equivalent to liver biopsy derived fibrosis staging in the prediction of clinical outcomes. **Will the committee acknowledge the limitations of using liver biopsy as the reference standard for diagnosing and characterising liver disease**
Perspectum Ltd	28	2.12 Using LMS/MRE to inform patient management	A number of prominent and experienced NHS hepatologists and radiologists from across the UK have communicated their desire confidentially with Perspectum to use Liver*MultiScan* in clinical practice to better inform their patient management. This is clearly at odds with the view given by the special committee members convened by NICE. Whilst there is clear variation in clinical practice across the UK, NICE should not deny forward-thinking clinicians the opportunity to provide more patient-friendly, less harmful care to their patients in favour of listening to clinicians who are entrenched in their own clinician-centric methods of clinical management. **Given that the NAFLD/NASH disease space guidelines (NG49) are scheduled for review in the coming months, Perspectum requests that the assessment is paused as new evidence and opinions considered in that appraisal may change the outcomes and results on the DAP59 assessment.**
Perspectum Ltd	29	Throughout	On the 1st August 2022, NICE stakeholders received an email stating that a number of NICE guidelines are being reviewed to see whether they need updated. One of those guidelines was Non-alcoholic fatty liver disease (NAFLD): assessment and management (NG49) **(published July 2016).** Perspectum are glad that this guideline is being reviewed and have registered as a stakeholder however feel that the publication of DAP59 should be postponed until after the NG49 review and/or update. There are many sections within the DAP59 scope, and DAR that rely on information from NG49 including utility values for the economic assessment, clinician recommendation for treatment and diagnostic test accuracy data highlighting the disease space's current 'gold

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			standard'. Should this information be updated in the coming months, it then renders the outcome of DAP59 futile. In addition, given there has been a great deal of research in the NAFLD and NASH space since the publication of NG49 (NASH vs fibrosis staging and upcoming medication and treatment), this will provide additional insight to the EAG and committee members that the current NG49 lacks. **Perspectum request, that if an appropriate assessment for DAP59 cannot be provided, guidance publication is suspended until after NG49 has been reviewed and updated as to aid a more thorough assessment of MRI based technologies for the assessment for NAFLD in the future.**
Perspectum Ltd	30	Additional evidence	Perspectum has performed a Freedom of Information analysis in addition to a review of publicly available sources (See FOI Summary 26Sep2022). The analysis highlighted that the cost of NAFLD related biopsies is more expensive than **all** liver MRIs in the past five years, irrespective of the indication of the liver MRI (E.g., liver cancer, gallstones etc). **Perspectum request that the EAG update their model to account for findings from the FOI summary and present the findings in the upcoming committee meetings.**

FOI requests and Waiting Time Summary

This summary has been written using Freedom of Information requests that were sent to the following NHS trusts: 1) University Hospital Southampton NHS Foundation Trust, 2) University College London Hospital NHS Foundation Trust, 3) Royal Free London NHS Foundation Trust, 4) South Warwickshire NHS Foundation Trust, 5) Nottingham University Hospitals NHS Trust and 6) Leeds Teaching Hospitals NHS Trust. Additional information was gathered from the Gastrointestinal and Liver services information from the NHS website and the 'My Planned Care' section of the NHS website. Costs have been calculated using publicly available NHS tariff costs for each appropriate year.

The cost of NAFLD related biopsies is more expensive than all liver MRIs in the past five years

Since 2017, the number of liver biopsies due to Non-alcoholic Fatty Liver Disease (NAFLD) have cost the above six NHS trusts a total of £576,509.43 for 484 biopsies. The total cost of liver MRI (regardless of liver aetiology) since 2017 for the same trusts was £305,975.80 for 2,731 MRI scans. If these 484 biopsies were replaced with liver MRI, the additional cost would be £54,348.15, resulting in a total of £360,323.95 for 3,215 MRI scans to the selected NHS trusts. If 100% of the NAFLD related biopsies in these 6 trusts since 2017 (484) had been replaced with liver MRI and Liver*MultiScan*, it would cost £150,664.15, providing a cost saving of £425,845.29 to the NHS.

If, the 2,731 patients having a liver MRI in these six NHS trusts, regardless of liver aetiology, had a Liver*MultiScan* in addition to their MRI it would cost £849,530.17 (£311.02 per patient). The per patient cost of performing a liver biopsy within these trusts for suspected NAFLD is £1,191.14. On a per patient basis, this would result in a costs savings of £880.11 to the NHS compared to performing a liver biopsy on these patients.

Biopsy refusal occurs within NHS trusts and therefore should be acknowledged in NICE analysis

In recent literature, the biopsy refusal rate has been reported as approximately 25%, (Ratziu et al., 2022) and biopsy refusal rate was provided in recent FOI requests. This has not been considered in the EAG analysis despite there a published record of biopsy being refused within the NHS.

The waiting time within the NHS, especially in the Gastrointestinal and Liver services have not been considered within the EAG analysis

The 'My Planned Care' section of the NHS website displays waiting times for services offered in NHS trusts across England. The waiting times displayed are the 1) average waiting time for first outpatient appointment the hospital for this speciality and 2) average waiting time for treatment at the hospital for this speciality. The maximum waiting time in the Gastroenterology speciality displayed is in the Midlands in the United Lincolnshire Hospitals NHS Trust where it will take 38 weeks to get an initial outpatient appointment and 35 weeks to get treatment within the Gastroenterology speciality.

These long waiting times are not isolated to the Midlands. The table below shows the highest waiting times for each of the seven regions across the England.

Table 1: NHS waiting times in English regions, search completed 13th September 2022

Region	Trust	Average waiting time for first outpatient appointment (weeks)	Average waiting time for treatment (weeks)

East of England	East and North Hertfordshire NHS Trust	32	29
North West	Countess of Chester Hospital NHS Foundation Trust	28	28
South East	University Hospitals Sussex Foundation Trust	27	26
Midlands	United Lincolnshire Hospitals NHS Trust	38	35
South West	Royal United Hospitals Bath NHS Foundation Trust	26	25
London	Lewisham and Greenwich NHS Trust	19	19
North East and Yorkshire	Harrogate and District NHS Foundation trust	20	21

The longest waiting times for a Trust with a Specialist Committee member for DAP59 was University College London Hospitals NHS Foundation Trust (outpatient appointment: 15 weeks, treatment: 19 weeks). These current waiting times should be considered within the analysis and the potential that Liver*MultiScan* has to alleviate these waiting times.

Throughout the NICE DAP59 assessment, there has been mention of the pressure that Liver*MultiScan* can add to the NHS, however, no data has been collected by the EAG looking specifically into the burden that liver biopsy services have on English NHS trusts.

References

1. Ratziu V, et al. An international survey on patterns of practice in NAFLD and expectations for therapies – The POP-NEXT study. 2022: 00: 1-12. DOI: 10.1002/hep.32500