Liver disease (non-alcoholic fatty) [NAFLD]

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Children's Liver Disease Foundation	General	General	General	CLDF believe it is positive that the initial research has highlighted the need for further studies looking into pharmacological treatments in children and young people with NAFLD and research to confirm testing which should be used for children and young people. There is an urgent need to understand the best methodology to test those with NAFLD as there is currently significant variation in practice	Thank you for your comment.
Children's Liver Disease Foundation	Short	3	6&7	NAFLD is recommended to be suspected in patients with type 2 diabetes or metabolic disorder. Children with NAFLD won't necessarily have developed type 2 diabetes, despite being at risk of doing so, particularly when very young. Should there be alternative advice for children?	Thank you for your comment. As is detailed in section 5.6 linking the evidence to the recommendations in the full guideline, unfortunately there was no cohort evidence identified for the paediatric population. However, the GDG agreed that there was no specific reason to suggest that these risk factors (diabetes and metabolic syndrome) would differ in a younger population and therefore agreed to extrapolate the evidence from adult populations to the younger age group. Recognising the importance of this area, the GDG made a high-priority research recommendation for further investigation into risk factors for NAFLD in children and young people. To confirm this assumption.
Children's Liver Disease Foundation	Full	50		Waist circumference was found to be a risk factor for NAFLD, could this included within the guideline regarding testing? 3 of the studies included supported the recommendation of re metabolic syndrome and 2 for waist circumference therefore could waist circumference be used as an indicator for testing for NAFLD? Equally if around 40% of obese children have NAFLD could obesity be the basis of testing?	Thank you for your comment. Waist circumference was considered a potential risk factor by the GDG and it was therefore outlined in the review protocol. The clinical evidence on waist circumference as a risk factor was considered in the economic model alongside the other risk factors listed in the review protocol. However, as explained in the section 'trade-off between net clinical effects and costs in section 5.6 in the full guideline the GDG agreed that if testing for NAFLD was provided it should be prioritised to those groups at highest risk of having or developing NAFLD (people with type 2 diabetes or metabolic syndrome). No evidence was identified for waist circumference in children.
Children's Liver Disease Foundation	Full	5.3		In our experience individuals with NAFLD are difficult to engage with – is there any evidence surrounding this/guidance which could be shared?	Thank you for your comment. No specific evidence review was conducted in this area and as such we are unable to make specific recommendations in this regard.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	General	General	Our comments focus on the application of the guideline to children and young people with suspected or definite NAFLD. We wish to highlight the differences that exist in children and young people with NAFLD compared to adults, in particular the histological difference (type 2 NASH in 50-70% of children, which is associated with more aggressive disease). In addition, physiology of growth in children may limit application of markers of fibrosis. Furthermore, the guideline scope appears to be very limited, being applicable only to those with type 2 diabetes or metabolic syndrome. This should be emphasised in the title.	Thank you for your comment. Throughout the development of this guideline the GDG has been mindful of the differences between children and young people, and adults. The GDG membership included a consultant paediatric hepatologist and a paediatric liver modern matron to ensure that considerations for children and young people were taken into account. At the start of guideline development, the GDG stratified many of the review question protocols based on these 2 populations. The corresponding evidence reviews have therefore presented evidence separately for children and young people, and for adults, which has led to the development of separate recommendations where appropriate. With respect to the guideline scope, this was not limited to people with type 2 diabetes and metabolic syndrome. These are the risk factors indicating which people should be suspected of having NAFLD as a result of the evidence reviewed in chapter 5 of the full guideline.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	General	General	There is very limited data on the application of ELF in children and young people. A single study has not been further validated (Nobili 2009). This included 112 patients but of these only 9 children had fibrosis of F3 or above - (the severity of fibrosis which is deemed significant by the GDG). Though they undertook a mathematical model of a theoretical cohort of 1000 children – the reason to do this was that there were only 9 children with significant fibrosis in the cohort! There is no validation of ELF in paediatric NAFLD outside this original cohort. Thus the recommendation for ELF is based on the differential values of 9 children with significant fibrosis thus real risk of sample bias. In addition ALL of these 112 children were Caucasian and this is not what we see in clinical practice – only about 50% of our NAFLD population are Caucasian – remainder are mainly Asian children in which there has been no work on ELF to my knowledge. We suggest ELF is removed as a recommendation for diagnosis or monitoring of	Thank you for your comment. There was very limited evidence for any of the diagnostic tests identified in the review protocol and there are no tests validated for identifying advanced fibrosis in children and young people. Given how important it is to identify children and young people who have advanced fibrosis and are therefore in danger of developing advanced or end stage liver disease, the GDG felt the available evidence (alongside the clinical expertise of paediatric liver specialists on the guideline committee) suggested that the use of ELF at a threshold of 10.51 would be a useful tool to pick up those with advanced fibrosis who need to be identified early to avoid disease progression. Following stakeholder consultation this recommendation has been amended to: consider using ELF to test people for advanced fibrosis. The addition of the word 'consider' reflects the uncertainty in the evidence.

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				disease severity in children and young people until such time as it is validated.	
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	14	algorithm	We feel it is not appropriate to apply ELF in children and young people	Thank you for your comment. The GDG extensively discussed the available evidence, including the quality and these discussions are captured in the 'Recommendations and link to evidence' section 7.6 in the full guideline, as detailed in the boxes on the trade-off between clinical benefits and harms, the trade-off between net clinical effects and costs, and the quality of the evidence. Given how important it is to identify children and young people who have advanced fibrosis and are therefore in danger of developing advanced or end stage liver disease, the GDG felt the available evidence (alongside the clinical expertise of paediatric liver specialists on the guideline committee) suggested that the use of ELF at a threshold of 10.51 would be a useful tool to pick up those with advanced fibrosis who need to be identified early to avoid disease progression. Following stakeholder consultation this recommendation has been amended to: consider using ELF to test people for advanced fibrosis.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	16	2,3,4	The use of ELF score for testing people for advance fibrosis (recommendation 11) is not appropriate in children and young people	Thank you for your comment. The GDG extensively discussed the available evidence, including the quality and these discussions are captured in the 'Recommendations and link to evidence' section 7.6 in the full guideline, as detailed in the boxes on the trade-off between clinical benefits and harms, the trade-off between net clinical effects and costs, and the quality of the evidence. Given how important it is to identify children and young people who have advanced fibrosis and are therefore in danger of developing advanced or end stage liver disease, the GDG felt the available evidence (alongside the clinical expertise of paediatric liver specialists on the guideline committee) suggested that the use of ELF at a threshold of 10.51 would be a useful tool to pick up those with advanced fibrosis who need to be identified early to avoid disease progression. Following stakeholder consultation this recommendation has been amended to: consider using ELF to test children and young people for advanced fibrosis.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	16	5,6,7,8	Referral to specialist according to ELF score (recommendation 12) is not appropriate in children and young people	Thank you for your comment. Following stakeholder consultation this recommendation has been updated to clarify that this test would only be happening in tertiary care in the case of children and young people. The recommendation referring to a hepatology specialist has been added to the earlier recommendation on using ultrasound to identify NAFLD in a paediatric population. The algorithm has been updated accordingly to reflect this change.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	16	13,14	Retesting ELF in children and young people with a score of <10.5 every two years (recommendation 14) is not appropriate in children and young people as no information exists on whether this gives a true longitudinal measure of disease progress rather than physiological change,	Thank you for your comment. In the section on trade-off between clinical benefits and harms in the 'Recommendations and link to evidence' section for the monitoring chapter (section 8.6 in the full guideline) it is noted that "there was concern that children and young people are rapidly developing and experiencing hormonal changes which may affect their risk of developing NAFLD. Furthermore type and volume of food intake and type and frequency of physical activity undertaken changes immensely in younger people over short periods of time." Due to these reasons the GDG decided to decrease from the evidence for a 6 year retesting frequency in adults to 3 years in the case of children and young people as warranted, based on expert opinion, so as not to miss the development of NAFLD.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	119	box	Recommendation 11 and 12: comments given above (comment 4 (ID20) and comment 5 (ID21))	Thank you for your comment. The GDG extensively discussed the available evidence, including the quality and these discussions are captured in the 'Recommendations and link to evidence' section 7.6 in the full guideline, as detailed in the boxes on the trade-off between clinical benefits and harms, the trade-off between net clinical effects and costs, and the quality of the evidence. Given how important it is to identify children and young people who have advanced fibrosis and are therefore in danger of developing advanced or end stage liver disease, the GDG felt the available evidence (alongside the clinical expertise of paediatric liver specialists on

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					the guideline committee) suggested that the use of ELF at a threshold of 10.51 would be a useful tool to pick up those with advanced fibrosis who need to be identified early to avoid disease progression. Following stakeholder consultation recommendation 1.1.6 in the NICE short guideline has been amended to: consider using ELF to test children and young people for advanced fibrosis. Following stakeholder consultation recommendation 1.1.6 has been updated to clarify that this test would only be happening in tertiary care in the case of children and young people. The recommendation referring to a hepatology specialist has been added to the earlier recommendation on using ultrasound to identify NAFLD in a paediatric population. The algorithm has been updated accordingly to reflect this change.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	132	box	Recommendation 14: see comment 6 (ID22) above	Thank you for your comment. In the section on trade-off between clinical benefits and harms in the 'Recommendations and link to evidence' section for the monitoring chapter (section 8.6 in the full guideline) it is noted that "there was concern that children and young people are rapidly developing and experiencing hormonal changes which may affect their risk of developing NAFLD. Furthermore type and volume of food intake and type and frequency of physical activity undertaken changes immensely in younger people over short periods of time." Due to these reasons the GDG decided to decrease the recommendation of a 5 year retesting frequency in adults to 3 years in the case of children and young people as warranted, based on expert opinion, so as not to miss the development of NAFLD.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	286		Recommendation 31: using ELF to monitor treatment use with vitamin E: we are concerned that there is no evidence to support the application of ELF in this respect.	Thank you for your comment. The objective of the monitoring review was to discover progression rates of NAFLD and subsequently who (in terms of severity of disease) should be monitored for progression and how often. We did not conduct a review on the most clinically and cost-effective tests to monitor response to pharmacological treatments for advanced fibrosis. Therefore, as discussed in the 'other considerations' section of 17.6 'Recommendations and link to evidence' in the full guideline, the GDG felt that it was the most logical and appropriate compromise to assess treatment response (to allow re-evaluation about whether the benefits of continuing therapy still outweighed potential risks) using the same non-invasive means recommended for identifying advanced fibrosis. This has now been worded as 'consider ELF' to reflect the evidence base. The GDG believed that since severe hepatic fibrosis has consistently been shown to be of prognostic value in people with NAFLD, these people require closest monitoring and have the most to gain from pharmacotherapy to slow or reverse the progression of fibrosis.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	General	General	The algorithm and section on diagnosis of NAFLD in children and young people states that "other suspected causes of fatty liver" need to be ruled out. However, it is implied that a diagnosis of NAFLD is a positive diagnosis. In children and young people we are concerned that children may be inappropriately given the diagnosis without an adequate consideration of other potential causes. We consider it imperative that other diagnoses (including metabolic disease, Wilson's disease and autoimmune liver disease) are considered, particularly when a rise in liver enzymes accompanies the presenting features, even when type 2 diabetes is present. Though the Guideline Development Group may feel that this is out-with the scope of this guideline, it needs clearly emphasising that in children and young people, particularly (but not exclusively) where liver enzymes are normal, other disorders must be considered. They may co-exist and mimic NAFLD.	Thank you for your comment. We have included a list of possible other causes of fatty liver in the final paragraph of the introduction in chapter 2. This list is also detailed in the other consideration section of the 'Recommendations and link to evidence' section 6.6 of the chapter on diagnosis of NAFLD in the full guideline. Clinicians have a responsibility to consider the relevant tests depending on the individual context and circumstance of the patient. As this is specifically the NAFLD guideline we cannot be inclusive of all tests to determine any possible cause of fatty liver.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	General	General	We question the evidence supporting three year follow up. We ask that the GDG takes into account the effects of growth and pubertal development on potential development and progression of NAFLD during this period.	Thank you for your comment. The 'Recommendations and link to evidence' section of chapter 6 in the full guideline details the GDG consideration of your points. In the section on trade-off between clinical benefits and harms it is noted that "there was concern that children and young people are rapidly developing and experiencing hormonal changes which may affect their risk of developing NAFLD. Furthermore type and volume of food intake and type and frequency of physical activity undertaken changes immensely in

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					younger people over short periods of time." Due to these reasons the GDG decided to decrease the 6-year retesting frequency in adults suggested by the economic modelling to 3 years in the case of children and young people as warranted, based on expert opinion, so as not to miss the development of NAFLD.
British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)	Full	General	General	The focus of this guidance is how to investigate for NAFLD and manage a patient with type 2 diabetes or metabolic syndrome, based on these being risk factors in adults. It would be extremely helpful if it is stated clearly at the outset that this guideline has not been validated in other scenarios (eg obesity without metabolic syndrome).	Thank you for your comment. Please note the guideline scope is not limited to managing people with type 2 diabetes or metabolic syndrome. A review was undertaken to identify which risk factors indicated people who should be suspected of NAFLD, which informed this recommendation. The guideline also covers the diagnosis, monitoring and treatment of NAFLD (diagnosed by any means) which are not limited to people with NAFLD and type 2 diabetes or metabolic syndrome.
Royal College of Paediatrics and Child Health	General	General	General	Thank you for inviting the Royal College of Paediatrics and Child Health to comment on the draft guideline consultation for Liver disease (non-alcoholic fatty [NAFLD]). We have not received any responses for this consultation.	Thank you for your comment.
University Hospital Birmingham NHS FT	Full	78	1	We are concerned that the Fatty Liver Index (FLI) has been suggested as the diagnostic test of choice for NAFLD. We know of no evidence that ultrasound (US) is so inferior to FLI that it should be left out of diagnostic algorithms for NAFLD altogether. Our preference would be to have the choice to use either FLI or US in the diagnosis of NAFLD.	Thank you for your comment. The GDG extensively discussed the available evidence, including the quality and these discussions are captured in the 'Recommendations and link to evidence' section 6.6 in the full guideline, as detailed in the boxes on the trade-off between clinical benefits and harms, the trade-off between net clinical effects and costs, and the quality of the evidence. The GDG explored the robustness of the original economic analysis by conducting extensive sensitivity analysis. While ultrasound is not diagnostically inferior to FLI, it is however much more expensive than FLI. Therefore it is very unlikely that using ultrasound for diagnosis of NAFLD could rank higher in terms of cost effectiveness compared to FLI. However, due to variation in the cost-effectiveness results for all tests under certain scenarios and uncertainty in the underlying evidence base (FLI diagnostic accuracy), testing for NAFLD was not recommended by the GDG and this recommendation has been replaced with a high priority research recommendation to inform future updates of the guideline.
University Hospital Birmingham NHS FT	Full	116	5	We are also concerned about the strong recommendation for using the Enhanced Liver Fibrosis (ELF) test in place of Fibroscan for assessing the severity of fibrosis. Whilst sending off a blood test in primary care may be easier than accessing a community Fibroscan, we know of no evidence that one mode of assessment is superior to the other. Indeed, whilst performance is broadly similar for advanced fibrosis, Fibroscan is superior to ELF in terms of defining lower levels of fibrosis. Therefore, we strongly believe that if local arrangements exist, then there should be a choice to use either ELF or Fibroscan.	Thank you for your comment. A systematic review and diagnostic meta-analysis were conducted for this review including any evidence on the diagnostic accuracy of non-invasive tests that met the review protocol (Appendix C in the full appendices). The clinical evidence from this review was taken into account in an original cost-utility analysis (detail in Appendix N in the full appendices). This analysis found that ELF is superior to all other non-invasive tests with respect to both clinical and cost-effectiveness. This is discussed in the 'trade-off between net clinical effects and costs in the 'Recommendations and link to evidence' section 7.6 in the full guideline. We looked for evidence regarding other stages of fibrosis and NASH, but there was no sufficiently applicable evidence available. As discussed in the 'trade-off between clinical benefits and harms' section of the same table, the GDG noted that people with advanced fibrosis are much more likely to have NASH, and hence to be suitable for pharmacological treatment. Therefore the GDG concluded that no assessment tools for diagnosing lower levels of fibrosis would be recommended for use based on the available evidence and they were therefore not included in the economic modelling. The question being examined in the modelling was therefore the most clinically and cost-effective test for advanced fibrosis, and this was found to be ELF, which has considerably better diagnostic accuracy with regard to F3 fibrosis than transient elastography ('Fibroscan'). However, we note that the evidence base for ELF is based on relatively small populations and therefore we have reworded this recommendation to 'consider ELF' to reflect the evidence base.

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University Hospital Birmingham NHS FT	Full	130	3	We also feel that Fibroscan could be used as an alternative to ELF for monitoring progression of NAFLD for the same reasons as discussed in (2).	Thank you for your comment. A systematic review and diagnostic meta-analysis were conducted for this review including any evidence on the diagnostic accuracy of non-invasive tests that met the review protocol (Appendix C in the full appendices). The clinical evidence from this review was taken into account in an original cost-utility analysis (detail in Appendix N in the full appendices). This analysis found that ELF is superior to all other non-invasive tests with respect to both clinical and cost-effectiveness. This is discussed in the 'trade-off between net clinical effects and costs in the 'Recommendations and link to evidence' section 7.6 in the full guideline. However, we note that the evidence base for ELF is based on relatively small populations and therefore we have reworded this recommendation to 'consider ELF' to reflect the evidence base. As discussed in the 'trade-off between clinical benefits and harms' section of the same table, members of the GDG questioned the benefit of attempting to identify all people with any fibrosis (including lower levels of fibrosis) as evidence suggests that it is only those with advanced fibrosis (greater than or equal to F3) who merit the closest monitoring and who are at greatest risk for complications and disease progression. The GDG also noted that people with advanced fibrosis are much more likely to have NASH, and hence to be suitable for pharmacological treatment. Therefore the GDG concluded that no assessment tools for diagnosing lower levels of fibrosis would be recommended for use based on the available evidence and they were therefore not included in the economic modelling. The question being examined in the modelling was therefore the most clinically and cost-effective test for advanced fibrosis, and this was found to be ELF, which has considerably better diagnostic accuracy with regard to F3 fibrosis than transient elastography ('Fibroscan').
University Hospital Birmingham NHS FT	Full	169	14	We are not convinced that the evidence for probiotics in NAFLD is strong enough to make the recommendation in this section of the document. The very modest weight reduction outlined (<5%) and reduction of liver fat in particular may be of no proven benefit in limiting progression of NAFLD.	Thank you for your comment. Following stakeholder consultation we have removed the recommendations relating to probiotics from the guideline.
University Hospital Birmingham NHS FT	Full	206	16	In contrast to our Statement in (4), we believe that the evidence for lifestyle modification in NAFLD is very strong. Although, this is recommended in the guidelines, it is often not addressed appropriately in clinical practice and our concern is that since implication of lifestyle modification is challenging, it might be superseded by the suggestion that patients could, for example, use probiotics as a first line treatment for NAFLD, avoiding the need for lifestyle change.	Thank you for your comment. The GDG agree that lifestyle modification is a very important part of the management of NAFLD. Following stakeholder consultation we have removed the recommendations relating to probiotics from the guideline.
NHS England				Thank you for the opportunity to comment on the above Clinical Guideline. I wish to confirm that NHS England has no substantive comments to make in regards to this consultation.	Thank you for your comment.
Perspectum Diagnostics Ltd	General	-	-	We consider it a limitation that the current draft guidelines lack any diagnostic recommendations on the assessment and management of fibrosis, other than advanced fibrosis.	Thank you for your comment. We looked for evidence regarding other stages of fibrosis and NASH, but there was no sufficiently applicable evidence available.
Perspectum Diagnostics Ltd	General	-	-	The original scope laid out in Appendix A states that these guidelines will address identification of NAFLD. We are surprised to see that final recommendations appear to have limited the scope of Question 1 to an identification of risk factors only, and not NAFLD itself.	Thank you for your comment. Question 1 was focussed on identifying the most clinically effective risk factors for NAFLD, to identify in whom to suspect NAFLD. From this evidence review (please see chapter 5 in the full guideline for full details of the evidence) type 2 diabetes and metabolic syndrome were identified as the risk factors. We undertook a review to determine the best non-invasive test to identify NAFLD (chapter 6), however due to the uncertainty in the evidence base a recommendation could not be made. The GDG made a high priority research recommendation on the topic of diagnosis of NAFLD to inform future updates of this guideline.
Perspectum Diagnostics Ltd	General	-	-	We are concerned that these guidelines have not included all the relevant data pertaining to imaging modalities for the non-invasive assessment of liver disease, which will limit the impact these guidelines are likely to have on clinical practice. In this regard,	Thank you for your comment. With respect to the two articles that you have suggested for inclusion:

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				we would like to draw the panel's attention to two publications that have not been included as part of either the clinical review or original economic modelling performed in the development of these guidelines: 1) A publication by Banerjee, 2014, J Hepatol. 60:69-77, which describes the clinical validation of novel multiparametric MR imaging modality for assessment of chronic liver disease. This publication appears to have been identified in the clinical evidence search, but screened out of selection, based on a perceived ineligibility (see comment 12, below). We are concerned that this may represent an error of judgement, or potentially be an indication of selection bias. Exclusion of this publication precludes analysis of highly relevant clinical data of a regulatory cleared (CE marked and FDA 510k) diagnostic tool that is available for clinical use. We consider it a short-coming of these guidelines that this imaging modality has not been included in the list of index tests or diagnostic strategies assessed (Full Guidelines, Table 23, p84-85) as either a stand-alone imaging technique, or as supporting evidence for the diagnostic accuracy of MRI in fibrosis, including advanced fibrosis (Full Guidelines, Tables 27-30, p96 - p106). 2) A publication by Pavlides et al., 2015, J Hepatol, 64:308-315, e-publication online. While this study was published in November 2015 after the 27 August 2015 cut-off as advised by the Guidelines Commissioning Manager, data published after the search date should be highlighted for inclusion if it is of particular clinical significance or potential impact on the draft guidelines. We consider this publication to provide critical evidence relevant to the diagnosis and management, concerning both the clinical and cost-effectiveness analysis performed. In brief, the publication provides clinical evidence of the diagnostic and prognostic accuracy of multiparametric MR imaging analysis in a cohort of 112 patients with chronic liver disease, of which n=39 had biopsy proven NAFLD. The study uses multiparametric MR imaging to characterise liver tissue, quantifying liver fat, liver iron (T2*), and fibro/inflammation (cT1), which was shown to have a 100% NPV in patients, irrespective of disease aetiology. This diagnostic tool is the only non-invasive imaging method that has been shown to accurately discriminate between intermediate stages of fibrosis. Furthermore, it is the only diagnostic imaging test which has been shown to predict clinical outcomes in general secondary care liver patients, including NAFLD (see Pavlides et al. 2015). While further clinical data may be required to support a full NICE recommendation, it is nonetheless critical data that we consider should be included in the clinical evidence review. We would strongly urge the GDG to include this data when making final guideline recommendations, in particular in response to these review questions 2-4.	1) Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. 2) As you mention Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1 in the full guideline). However we have taken the time to evaluate the paper and can inform you that it would be excluded for the following reasons: the primary outcome for this study is all-cause mortality and liver related clinical events (liver-related death, HCC or hepatic decompensation) and not diagnostic accuracy of the tool for steatosis in those with suspected NAFLD or advanced fibrosis in those with diagnosed NAFLD. Therefore the paper does not supply sufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. Secondly fibrosis was measured using the Ishak score not the Brunt scoring system and therefore does not match our protocol with respect to the reference standard.
Perspectum Diagnostics Ltd	General	-	-	By restricting the scope of these guidelines to exclude incidentally found abnormal liver blood tests, we are concerned the new guidelines will have only limited impact on current clinical practice as they do not provide clear guidance on how to rule out NAFLD that will meaningfully effect change in current practice, acknowledged by the authors on page 19, lines 24-26 to be primarily through incidental findings.	Thank you for your comment. The scope of this guideline is not wide enough to encompass how to investigate any findings of abnormal liver blood tests, as that is a much broader scope. This guideline was commissioned to review the assessment and management of NAFLD. Those who have been identified with NAFLD through incidental findings have not been excluded and will enter the guideline pathway as shown in the algorithm.
Perspectum Diagnostics Ltd	Full	14	2	This summary algorithm could benefit from clearer indication as to when diagnostic test(s) for cirrhosis should be considered in the assessment and monitoring of NALFD patients. The diagram directs physicians to refer to cirrhosis guidelines, following rule-out of alcohol-related liver disease. However, the draft cirrhosis guidelines recommend testing for cirrhosis only after NAFLD has been confirmed. The stratification of patients following NAFLD diagnosis fails to clearly indicate how those with a positive FLI / abnormal ultrasound should be managed and at what point testing for advanced fibrosis (F3 or above) should be performed alongside recommendations for the non-pharmacological management of NAFLD. Aesthetically, the diagram may also benefit	Thank you for your comment. We have amended the beginning of the algorithm to clarify that a patient would only enter this pathway if it was possible to rule out alcohol-related liver disease, and that the referral to the cirrhosis guideline at the start of the algorithm would only be for those in whom you could not rule out ALD. The cirrhosis guideline does not only recommend testing for cirrhosis after NAFLD has been confirmed. People with confirmed NAFLD and advanced fibrosis are only 1 of 5 populations that the cirrhosis guideline covers (including men and women who drink respectively 50 or 35 units of alcohol per week over a period of several months).

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				from clearer indication of where management is in handled in primary vs. secondary care.	With respect to your other concerns we believe that the algorithm is clear in how an adult would move through the NAFLD pathway from receiving non-pharmacological management following a diagnosis of NAFLD, to being tested for advanced fibrosis, for which if confirmed they would be referred to a specialist in hepatology and offered pharmacological management.
Perspectum Diagnostics Ltd	Full	15	8	This recommendation falls short of providing a clear recommendation on how to stratify patients with suspected NAFLD at the point of care. Cross-referencing to the NICE guidelines for cirrhosis at this point in the diagnostic algorithm creates a circular loop, as the draft recommendations for cirrhosis testing in NAFLD patients stipulate that the patient must already have been diagnosed with NAFLD and advanced fibrosis using the enhanced liver test (ELF). Hence this introduces a lack clarity regarding best-practice for how to best proceed with a diagnosis for NAFLD following rule-out of alcohol-related liver disease.	Thank you for your comment. We have amended the beginning of the algorithm to clarify that a patient would only enter the NAFLD pathway if it was possible to rule out alcohol-related liver disease, and that the referral to the cirrhosis guideline at the start of the algorithm would only be for those in whom you could not rule out alcohol related liver disease. The cirrhosis guideline does not recommend testing for cirrhosis only for those for whom NAFLD has been confirmed. People with confirmed NAFLD and advanced fibrosis are only 1 of 5 possible populations that the cirrhosis guideline covers (including men and women who drink respectively 50 or 35 units of alcohol per week over a period of several months). With respect to your other concerns we believe that the algorithm is clear in how an adult would move through the NAFLD pathway from receiving non-pharmacological management following a diagnosis of NAFLD, to being tested for advanced fibrosis, for which if confirmed they would be referred to a specialist in hepatology and offered pharmacological management.
Perspectum Diagnostics Ltd	Full	15	12	This recommendation would benefit from a definition on the components of the metabolic syndrome a patient must have to qualify for testing.	Thank you for your comment. Metabolic syndrome is defined in the guideline introduction (page 19 in the full guideline) as: central obesity (excessive abdominal fat), insulin resistance or type 2 diabetes, hypertension and dyslipidaemia. We have added this definition to the glossary.
Perspectum Diagnostics Ltd	Full	15	16-21	We are concerned the algorithm for assessment and monitoring of NAFLD relies too heavily on the fatty liver index (FLI). Both the reliability and applicability of the FLI diagnostic tool for NALFD in clinical practice is disputed in the literature, yet there is little to no discussion or acknowledgement of this caveat in either the short or full guidelines. Moreover, this recommendation appears to be based only a small number of studies of low or very low quality evidence. The diagnostic performance of the FLI has been primarily validated against ultrasound, which has poorer sensitivity and specificity for accurately determining liver fat content compared to other diagnostic tests. To our knowledge, the validation of FLI was limited to Northern Italian and Chinese cohorts, which are likely to have inherent difference to UK population – this should be acknowledged or discussed in the recommendations. Notably, a recent editorial in AP&T has explicitly recommended against use of FLI as a tool for identifying presence of NAFLD (see Vanni and Bugianesi, AP&T, 2015).	Thank you for your comment. Following consultation and further discussion regarding the uncertainty of the evidence base and specificity of FLI, the recommendation for FLI has been removed and replaced with a high priority research recommendation to inform future updates of this guideline. The guideline and algorithm have been updated accordingly. Regarding the review considerations, As you can see in the review protocol referenced in Table 17 in the full guideline and detailed in Appendix C in the full appendices, the GDG only accepted papers that compared the performance of FLI with the gold standard of liver biopsy. With respect to your comment about the validation in different ethnicities, FLI has been validated in a number of different populations (including different European populations, Asian and North American) with good performance in all; for instance, see: http://onlinelibrary.wiley.com/doi/10.1111/apt.13063/full . The populations of the papers included in this review for FLI were French and Canadian. Furthermore, the GDG did not believe that there is reason to think that the components that make up FLI would expected to be different in different populations or that FLI should perform differently in different populations.
Perspectum Diagnostics Ltd	Full	15	22-32	There is insufficient evidence to recommend use of standard ultrasound as a method for excluding fatty liver disease in children and young people (CYP). The poor sensitivity of ultrasonographic imaging as a means of assessment in overweight and obese children is well documented in current scientific literature (see Vajro et al. J Pediatr Gastroenterol Nutr, 2012) and NICE guidelines should reflect this appropriately, perhaps with a caution attached to this recommendation for rule-out of fatty liver disease based on ultrasound alone.	Thank you for your comment. The GDG extensively discussed the available evidence, including the quality and these discussions are captured in the 'Recommendations and link to evidence' section 6.6 in the full guideline. The paper you reference (Vajro et al. 2012) was not included in the review as it did not fit the protocol for inclusion in the systematic review and meta-analysis conducted on data for the diagnostic accuracy of non-invasive tests (including ultrasound) for detecting fatty liver in children and young people. The Vajro paper is excluded for reasons relating to incorrect study design. The review protocol described inclusion criteria for diagnostic accuracy studies. The Vajro paper is a position paper detailing a literature review rather than a paper on primary research or a systematic

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					review providing data on the diagnostic accuracy of ultrasound that could be extracted and analysed. As detailed in the 'Recommendations and link to evidence' section in the full guideline on the trade-off between clinical benefits and harms, the GDG is aware that very few of the diagnostic techniques under investigation in this review (in fact only one) have been validated within cohorts of children and young people with NAFLD. Based on the available evidence and their clinical expertise the GDG did not think it was appropriate to extrapolate the performance of FLI (the most cost-effective test for adults) to the paediatric population given that it includes a measurement of waist circumference. Ultrasound was the next most cost-effective test in adults and the GDG agreed it was widely accepted as an appropriate diagnostic tool for children and young people as there was no clinical reason to believe that the performance would differ in a younger population. The GDG therefore recommended that ultrasound should be used as the preferred diagnostic test for NAFLD in children and young people at highest-risk (those with diabetes or metabolic syndrome).
Perspectum Diagnostics Ltd	Full	16	1-14	This recommendation presents a risk to patients as the stratification for referral to specialist relies on a single, patented, propriety serum biomarker panel, the European Liver Fibrosis (ELF) test. It is unclear why the framework of this recommendation has been limited to a single, commercially available blood test, which has been reported in the literature to have a specificity of only 41% and AUROC = 0.80 for the detection of severe fibrosis (Rosenberg 2004, Gastroenterology, 127:1704-1713). The cost and limited availability of such proprietary serum biomarkers has been highlighted by the European Association for the Study of Liver Disease in their clinical practice guidelines on non-invasive test of liver disease (EASL; 2015. J Hepatol. 63:237-264). We are aware of previous supply issues regarding availability of the ELF from Siemens in the UK and Ireland, which may make this recommendation difficult to implement. In addition, this test is non-specific and given the risk of comorbidities and extra-hepatic complications, this poses a higher risk of incorrect/misdiagnosis. The lead biostatistician for both the Cochrane Collaboration NIHR Health Technology Assessment Programme, is known to have expressed major concerns about the validity of the ELF test, which have been widely discussed and documented in NHS and government fora. It is also surprising that the GDG has provided recommendations for monitoring NAFLD progression based primarily on the ELF test, given the low quality evidence identified in support of the prognostic value of this test, and risk of bias flagged according to QUADAS-2.	Thank you for your comment. The GDG extensively discussed the available evidence for all of the non-invasive tests listed in the review protocol (Appendix C), including the quality of the evidence and these discussions are captured in the 'Recommendations and link to evidence' section 7.6 in the full guideline. With respect to the reference you provided (Rosenberg 2004) the accuracy figures you mention (based we presume on the figures in row 2 in Table 2) are in relation to the performance of ELF in the whole cohort of patients with diverse chronic liver diseases (n=921 with adequate biopsy). As you will note in the protocol for the review question in this guideline (detailed in Appendix C in the full appendices), the population of interest was adults, children and young people already diagnosed with NAFLD. Table 5 of the Rosenberg 2004 paper lists the performance of ELF at different thresholds to detect advanced fibrosis (F3 and above) in a NAFLD specific population. This shows much higher accuracy (89% sensitivity and 96% specificity at a threshold of 0.375, and 78% sensitivity and 98% specificity at a threshold of 0.462). While this paper provides insufficient evidence for inclusion in the systematic review and diagnostic meta-analysis conducted for this review question, the reported performance is in line with the available evidence when looking at the population specified in the review protocol. The GDG are unaware of the supply issues that you refer to. Although analysis will need to be performed by a specialist laboratory, ELF can be requested from any laboratory at present, but is infrequently requested at present. We have acknowledged that the evidence informing the ELF recommendation is not high quality and therefore the recommendation has been reworded to 'consider ELF' to reflect the lower quality evidence.
Perspectum Diagnostics Ltd	Full	19	9	These statistics should be ideally referenced with relevance to UK population. The data is available from the UK BioBank and was presented to the Lancet Commission in Summer 2015.	Thank you for your comment. Appropriate references have been added.
Perspectum Diagnostics Ltd	Full	63	30	Review Question 2: We are concerned that a relevant publication (Banerjee, 2014, J Hepatol. 60:69-77) has been excluded from the clinical review of the diagnosis of NALFD. According to the NAFLD search strategies outlined in Appendix G, the Banerjee 2014 publication was identified, but excluded as the "*population does not match protocol*" as noted in Appendix M (Appendices, p578). We consider this to be an oversight as the publication appears to fulfil the criteria as detailed in the review protocol in Appendix C (Appendices, p32). Banjeree 2014 is a prospective, comparative, non-randomised clinical study (NCT01543646) comparing the diagnostic accuracy of	Thank you for your comment. Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore we could not calculate the 2×2 tables needed to analyse the results.

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				magnetic resonance (MR) imaging and spectroscopy in n=79 patients undergoing liver biopsy. The study cohort includes n=36 patients with steatohepatitis (45.6%), of which 5 had coexistent viral hepatitis. This patient population is similar in size and characteristics to other studies that have been included in the clinical review as detailed in Table 18, p65, for example; Dasarathy 2009 (n=73 patients; 28.8% NAFLD) and de Ledinghen 2012 (n=112 patients, NAFLD 25%). Considering only the n=36 patients with steatohepatitis identified in Banerjee 2014, this cohort size is still similar to other studies included in the clinical review, namely; Koelblinger 2012 (MRS; n=35), Marsman 2011 (MRI; n=36), and Urdzik 2012 (MRS; n = 35). It is notable that none of the three studies are in patients where NAFLD is the primary disease aetiology – indeed this is true of much of the clinical evidence included in the analysis, and so the heterogeneous population in Banerjee 2014 would not seem to be a grounds for exclusion. We encourage the GDG to include the data from Banerjee 2014 as part of this review question, as it provides a comparative assessment of hepatic steatosis measured with H^1 MRS against the Brunt standard of histological grading of hepatic lipid content (S0 – S3) that contributes to the body of data for assessment of steatosis and is relevant to both the clinical and health economic recommendations detailed in this Chapter. Furthermore, this publication is based on UK secondary care patient population so would appear to be well within scope.	
Perspectum Diagnostics Ltd	Full	74	18	We consider it a serious short-coming that these guidelines do not included multiparametric MR imaging analysis in the list of index tests or diagnostic strategies compared, with reasons as outlined in comment 3 and 12.	Thank you for your comment. Diagnostic accuracy evidence on all MR based techniques was sought in the systematic literature review. Multiparametric MRI was not excluded as a diagnostic strategy. No papers investigating the diagnostic accuracy of this tool were identified that met the requirements of the review protocols for diagnosing NAFLD or diagnosing the severity of NAFLD.
Perspectum Diagnostics Ltd	Full	76	21	Given the small number of studies, and moderate to low quality of evidence assessed, we recommend inclusion of Banerjee 2014 as a relevant clinical study reporting the diagnostic test accuracy of MRS for diagnosing steatosis ≥5% to strengthen the overall body of evidence supporting this recommendation. We are concerned that this diagnostic strategy has not been included for reasons as outlined in comment 3 and 12.	Thank you for your comment. Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool.
Perspectum Diagnostics Ltd	Full	77	8	Given the small number of studies, and moderate to low quality of evidence assessed, we recommend inclusion of Banerjee 2014 as relevant clinical study reporting the diagnostic test accuracy of MRS for diagnosing steatosis ≥30% to strengthen the overall body of evidence supporting this recommendation. We are concerned that diagnostic strategy has not been included for reasons as outlined in comment 3 and 12.	Thank you for your comment. Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool.
Perspectum Diagnostics Ltd	Full	77	24	To ensure these guidelines provide a comprehensive assessment of all available diagnostic tools, we recommend multiparametric MR be included as a diagnostic strategy for the detection of NAFLD, with reference to the clinical evidence from Banerjee 2014 and Pavlides 2015. We are concerned that this diagnostic strategy has not been included for reasons as outlined in comment 3 and 12.	Thank you for your comment. With respect to the two articles that you have suggested for inclusion: 1) Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool.

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					2) Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1 in the full guideline). However, we have taken the time to evaluate the paper and can inform you that it would be excluded for the following reasons: the primary outcome for this study is all-cause mortality and liver related clinical events (liver-related death, HCC or hepatic decompensation) and not diagnostic accuracy of the tool for steatosis in those with suspected NAFLD or advanced fibrosis in those with diagnosed NAFLD. Therefore the paper does not supply sufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. Secondly, fibrosis was measured using the Ishak score not the Brunt scoring system and therefore does not match our protocol with respect to the reference standard.
Perspectum Diagnostics Ltd	Full	84	13	Review Question 3: We are concerned that this question has not included all the relevant data pertaining to accuracy of available diagnostic tools for classifying the various stages of NAFLD. Firstly, the Banerjee 2014 publication (J Hepatol. 60:69-77), highlighted in comment number 3 and 12 above has been omitted. This publication describes a novel measure of hepatic fibrosis imaging – an iron-corrected T1 (cT1) mapping MR analysis. The clinical study shows comparative analysis of cT1 to histological fibrosis staging (Ishak F0-F6), and includes a subgroup analysis performed in n=36 patients with biopsy proven steatosis to compare MR data against NAFLD Fibrosis Stage (F0-F4). These data were critical to the MRC and Wellcome decisions to include liver assessment as part of UK BioBank as this was the first robust liver phenotyping method that could be deployed within UK healthcare settings. Statistical analysis of the AUROC, sensitivity and specificity have been reported and hence we consider this publication to have met the protocol requirements detailed in Appendix C (Appendices, p33). Secondly, we suggest that the GDG strongly consider including the Pavlides 2015 publication (detailed in comment number 2) in its clinical and economic evidence review.	Thank you for your comment. With respect to the two articles that you have suggested for inclusion: 1) Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. 2) Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1 in the full guideline). However, we have taken the time to evaluate the paper and can inform you that it would be excluded for the following reasons: the primary outcome for this study is all-cause mortality and liver related clinical events (liver-related death, HCC or hepatic decompensation) and not diagnostic accuracy of the tool for steatosis in those with suspected NAFLD or advanced fibrosis in those with diagnosed NAFLD. Therefore the paper does not supply sufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. Secondly fibrosis was measured using the Ishak score not the Brunt scoring system and therefore does not match our protocol with respect to the reference standard.
Perspectum Diagnostics Ltd	Full	85	21	Of the 18 studies identified in this clinical review, we note that almost all of these have been considered to provide only low quality evidence, with QUADAS-2 checklist often flagging a 'serious' or 'very serious' risk of bias. To ensure these guidelines provide a comprehensive assessment of all available diagnostic tools, we recommend inclusion of Banerjee 2014 and ideally Pavlides 2015 as relevant clinical studies reporting the diagnostic test accuracy and utility of multiparametric MRI for diagnosing NASH. We are concerned that this diagnostic strategy has not been included, reasons as outlined in comment 3, 12 and 17.	Thank you for your comment. With respect to the two articles that you have suggested for inclusion: 1) Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. 2) Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1 in the full guideline). However we have taken the time to evaluate the paper and can inform you that it would be excluded for the following reasons: the primary outcome for this study is all-cause mortality and liver related clinical events (liver-related death, HCC or hepatic decompensation) and not diagnostic accuracy of the tool for steatosis in those with suspected NAFLD or advanced fibrosis in those with diagnosed NAFLD. Therefore the paper does not supply sufficient data to populate the 2×2 tables

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					required to analyse the diagnostic accuracy of the tool. Secondly fibrosis was measured using the Ishak score not the Brunt scoring system and therefore does not match our protocol with respect to the reference standard.
Perspectum Diagnostics Ltd	Full	85	27 – 33	Of the 10 studies identified in this clinical review, we note that majority of these are of very low or low quality, with a 'serious' or 'very serious' risk of bias. We believe it the guidelines are incorrect to assert that there are no studies reporting the diagnostic test accuracy for diagnosing any fibrosis for MRI. We consider it a short-coming that the clinical evidence presented in Banerjee 2014 (outlined in comment 3 and 17) has not been included. To ensure these guidelines provide a comprehensive assessment of all available diagnostic tools, we would recommend inclusion of Banerjee 2014 and ideally Pavlides 2015 as relevant clinical studies reporting the diagnostic test accuracy and utility of multiparametric MRI for any fibrosis (greater than or equal to F1).	Thank you for your comment. With respect to the two articles that you have suggested for inclusion: 1) Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. 2) Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1 in the full guideline). However, we have taken the time to evaluate the paper and can inform you that it would be excluded for the following reasons: the primary outcome for this study is all-cause mortality and liver related clinical events (liver-related death, HCC or hepatic decompensation) and not diagnostic accuracy of the tool for steatosis in those with suspected NAFLD or advanced fibrosis in those with diagnosed NAFLD. Therefore the paper does not supply sufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. Secondly fibrosis was measured using the Ishak score not the Brunt scoring system and therefore does not match our protocol with respect to the reference standard.
Perspectum Diagnostics Ltd	Full	85	34	To ensure these guidelines provide a comprehensive assessment of all available diagnostic tools, we would recommend inclusion of Banerjee 2014 and ideally Pavlides 2015 as relevant clinical studies reporting the diagnostic test accuracy and utility of multiparametric MRI for any advanced fibrosis (greater than or equal to F3). Reasons as outlined in comment 3, 12 and 17.	Thank you for your comment. With respect to the two articles that you have suggested for inclusion: 1) Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. 2) Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1 in the full guideline). However we have taken the time to evaluate the paper and can inform you that it would be excluded for the following reasons: the primary outcome for this study is all-cause mortality and liver related clinical events (liver-related death, HCC or hepatic decompensation) and not diagnostic accuracy of the tool for steatosis in those with suspected NAFLD or advanced fibrosis in those with diagnosed NAFLD. Therefore the paper does not supply sufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. Secondly fibrosis was measured using the Ishak score not the Brunt scoring system and therefore does not match our protocol with respect to the reference standard.
Perspectum Diagnostics Ltd	Full	109	15	We are concerned that multiparametric MRI has not been included as a compared diagnostic strategy in the original cost-effectiveness analysis reported in these guidelines. We consider this to be a significant short-coming of an otherwise high quality and crucially important health economic evaluation. By excluding multiparametric MRI,	Thank you for your comment. Diagnostic accuracy evidence on all MR based techniques was sought in the systematic literature review. Multiparametric MRI was not excluded as a diagnostic strategy. No papers investigating the diagnostic accuracy of this tool were identified that met the requirements of the review protocols for diagnosing NAFLD or

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				and the relevant clinical evidence published in Banerjee 2014, this economic analysis falls short of providing a comprehensive analysis of all the diagnostic strategies available in the clinical practice in the UK today, which will limit the impact of these recommendations on clinical practice.	diagnosing the severity of NAFLD.
Perspectum Diagnostics Ltd	Full	110	28	As highlighted in comment 10 above, we have concerns regarding the high accuracy, sensitivity and specificity that has been attributed to ELF test.	Thank you for your comment. With respect to the reference you provided (Rosenberg 2004) the accuracy figures you mention (based we presume on the figures in row 2 in Table 2) are in relation to the performance of ELF in the whole cohort of patients with diverse chronic liver diseases (n=921 with adequate biopsy). As you will note in the protocol for the review question in this guideline (detailed in Appendix C in the full appendices), the population of interest was adults, children and young people already diagnosed with NAFLD. Table 5 of the Rosenberg 2004 paper lists the performance of ELF at different thresholds to detect advanced fibrosis (F3 and above) in a NAFLD specific population. This shows much higher accuracy (89% sensitivity and 96% specificity at a threshold of 0.375, and 78% sensitivity and 98% specificity at a threshold of 0.462). While this paper provides insufficient evidence for inclusion in the systematic review and diagnostic meta-analysis conducted for this review question, the reported performance is in line with the available evidence when looking at the population specified in the review protocol.
Perspectum Diagnostics Ltd	Full	112	3	We would recommend inclusion of Banerjee 2014 and ideally Pavlides 2015 as relevant clinical studies reporting the diagnostic test accuracy and utility of multiparametric MRI for diagnosing NASH. We are concerned that this diagnostic strategy has not been included for reasons as outlined in comment 3, 12 and 17.	Thank you for your comment. With respect to the two articles that you have suggested for inclusion: 1) Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. 2) As you mention Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1 in the full guideline). However we have taken the time to evaluate the paper and can inform you that it would be excluded for the following reasons: the primary outcome for this study is all-cause mortality and liver related clinical events (liver-related death, HCC or hepatic decompensation) and not diagnostic accuracy of the tool for steatosis in those with suspected NAFLD or advanced fibrosis in those with diagnosed NAFLD. Therefore the paper does not supply sufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. Secondly fibrosis was measured using the Ishak score not the Brunt scoring system and therefore does not match our protocol with respect to the reference standard.
Perspectum Diagnostics Ltd	Full	112	20	We would recommend inclusion of Banerjee 2014 and ideally Pavlides 2015 as relevant clinical studies reporting the diagnostic test accuracy and utility of multiparametric MRI for any fibrosis (greater than or equal to F1). We are concerned that this diagnostic strategy has not been included for reasons as outlined in comment 3, 12 and 17.	Thank you for your comment. With respect to the two articles that you have suggested for inclusion: 1) Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool.

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					2) As you mention Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1 in the full guideline). However, we have taken the time to evaluate the paper and can inform you that it would be excluded for the following reasons: the primary outcome for this study is all-cause mortality and liver related clinical events (liver-related death, HCC or hepatic decompensation) and not diagnostic accuracy of the tool for steatosis in those with suspected NAFLD or advanced fibrosis in those with diagnosed NAFLD. Therefore the paper does not supply sufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. Secondly, fibrosis was measured using the Ishak score not the Brunt scoring system and therefore does not match our protocol with respect to the reference standard.
Perspectum Diagnostics Ltd	Full	113	2	We would recommend inclusion of Banerjee 2014 and ideally Pavlides 2015 as relevant clinical studies reporting the diagnostic test accuracy and utility of multiparametric MRI for advanced fibrosis (greater than or equal to F3). We are concerned that this diagnostic strategy has not been included for reasons as outlined in comment 3, 12 and 17.	Thank you for your comment. With respect to the two articles that you have suggested for inclusion: 1) Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. 2) As you mention Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1 in the full guideline). However we have taken the time to evaluate the paper and can inform you that it would be excluded for the following reasons: the primary outcome for this study is all-cause mortality and liver related clinical events (liver-related death, HCC or hepatic decompensation) and not diagnostic accuracy of the tool for steatosis in those with suspected NAFLD or advanced fibrosis in those with diagnosed NAFLD. Therefore the paper does not supply sufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. Secondly fibrosis was measured using the Ishak score not the Brunt scoring system and therefore does not match our protocol with respect to the reference standard.
Perspectum Diagnostics Ltd	Full	115	31	As highlighted in comment 21, we are concerned that multiparametric MRI has not been included in the diagnostic strategies compared in the new cost-effectiveness analysis reported in these guidelines. We consider this to be a significant short-coming of an otherwise high quality and crucially important health economic evaluation. By excluding multiparametric MRI, and the relevant clinical evidence published in Banerjee 2014, this economic analysis falls short of providing a comprehensive analysis of all the diagnostic strategies available in the clinical practice in the UK today, which will limit the impact of these recommendations on clinical practice.	Thank you for your comment. Diagnostic accuracy evidence on all MR based techniques was sought in the systematic literature review. Multiparametric MRI was not excluded as a diagnostic strategy. No papers investigating the diagnostic accuracy of this tool were identified that met the requirements of the review protocols for diagnosing NAFLD or diagnosing the severity of NAFLD.
Perspectum Diagnostics Ltd	Full	121	3	This introduction lacks any discussion regarding the challenges and risks of monitoring NAFLD progression by serial liver biopsy.	Thank you for your comment. Detail has been added to the introduction of chapter 8 to clarify this.
Perspectum Diagnostics Ltd	Full	121	13	It is unclear why the selection criteria for clinical evidence has been limited to evidence where only paired biopsy data is available, as this is not explicitly stated in the review protocol and should be clarified if this is the case.	Thank you for your comment. This was an omission and has been updated accordingly. The GDG believes that paired biopsy studies offer some of the best available natural history data on the rate and risk factors associated with the progression of NAFLD. As no test for identifying NASH was identified and liver biopsy is widely accepted as the gold standard for measuring progression of NAFLD/NASH/fibrosis these were the most appropriate study designs to accept for inclusion.
Perspectum Diagnostics Ltd	Full	121	7	Review Question 8: Given the predominately low to moderate quality evidence reviewed to address the question of best practice for NAFLD patient monitoring, we recommend	Thank you for your comment. As previously noted the paper you have identified was published outside of the guideline cut-off for inclusion. However, the technical team has

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				inclusion of Pavlides 2015 as a highly relevant clinical study. As outlined in comment 3 and 17 above, this prospective clinical study shows the utility of multiparametric MRI as a prognostic tool for monitoring NAFLD progression in a cohort of 112 patients with chronic liver disease, including n=39 had biopsy proven NAFLD. While the study does not include paired biopsy data, outcomes for all patients are evaluated at a median of 27 months and compared to baseline characteristics, revealing a 100% NPV for liver-related incidents in patients with below a certain threshold value, as determined by multiparametric MR measure at baseline. Cox regression analysis of all measured variables of liver tissue characterisation, revealed an increase in the cumulative risk for developing clinical events with measured liver fibrosis and inflammation (LIF).	investigated the paper and can confirm it would not have been included in this review as it does not match the review protocol and does not provide any evidence on the outcome of interest in this review – progression of NAFLD to NASH, progression of NASH to NASH with fibrosis or progression of NASH with fibrosis to cirrhosis. This review was not focused on prediction of liver-related clinical events.
Perspectum Diagnostics Ltd	Short	3	10	See comment 6 (ID49) re: full guidelines (p15, line 8)	Thank you for your comment. We have amended the beginning of the algorithm to clarify that a patient would only enter the NAFLD pathway if it was possible to rule out alcohol-related liver disease, and that the referral to the cirrhosis guideline at the start of the algorithm would only be for those in whom you could not rule out ALD. The cirrhosis guideline does not recommend testing for cirrhosis only for those for whom NAFLD has been confirmed. People with confirmed NAFLD and advanced fibrosis are only 1 of 5 possible populations that the cirrhosis guideline covers (including men and women who drink respectively 50 or 35 units of alcohol per week over a period of several months). With respect to your other concerns we believe that the algorithm is clear in how an adult would move through the NAFLD pathway from receiving non-pharmacological management following a diagnosis by incidental findings, to being tested for advanced fibrosis, for which if confirmed they would be referred to a specialist in hepatology and offered pharmacological management.
Perspectum Diagnostics Ltd	Short	3	14	See comment 7 (ID50) re: full guidelines (p15, line 12)	Thank you for your comment. Metabolic syndrome is defined in the guideline introduction (page 19 in the full guideline) as: central obesity (excessive abdominal fat), insulin resistance or type 2 diabetes, hypertension and dyslipidaemia. We have added this definition to the glossary.
Perspectum Diagnostics Ltd	Short	4	2 - 9	See comment 8 (ID51) re: full guidelines (p15, line 16-21)	Thank you for your comment. The GDG extensively discussed the available evidence, including the quality and these discussions are captured in the 'Recommendations and link to evidence' section 6.6 in the full guideline. While you are correct that the clinical evidence for FLI was rated as low quality, you will notice that the entirety of the evidence for the all of the non-invasive tests in this review was rated at either low or very low quality. As you can see in the review protocol referenced in Table 17 and detailed in Appendix C in the full appendices, the GDG only accepted papers that compared the performance of FLI with the gold standard of liver biopsy. Thank you for referring us to the editorial. We disagree with your statement that this article explicitly recommends against the use of FLI as a tool for identifying the presence of NAFLD. It concludes by saying "although FLI can help with the detection of fatty liver, it should not be used as a tool for identifying the presence of NASH". This guideline is not recommending using FLI to identify NASH. However, following further consideration of the available evidence, the recommendation for FLI to diagnose NAFLD has been removed due to uncertainties in the evidence base, and a high priority research recommendation has been written in its place to further inform the evidence base.
Perspectum Diagnostics Ltd	Short	4	10-20	See comment 9 (ID52) in re: full guidelines (p225, line 22-32)	Thank you for your comment. The GDG extensively discussed the available evidence, including the quality and these discussions are captured in the 'Recommendations and link to evidence' section 6.6 in the full guideline. The paper you reference (Vajro et al., 2012) was not included in the review as it did not fit the protocol for inclusion in the systematic review and meta-analysis conducted on data for the diagnostic accuracy of non-invasive

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					tests (including ultrasound) for detecting fatty liver in children and young people. As detailed in the 'Recommendations and link to evidence' section on the trade-off between clinical benefits and harms in the full guideline, the GDG is aware that very few of the diagnostic techniques under investigation in this review (in fact only one) have been validated within cohorts of children and young people with NAFLD. Based on the available evidence and their clinical expertise the GDG did not think it was appropriate to extrapolate the performance of FLI (the most cost-effective test for adults) to the paediatric population given that it includes a measurement of waist circumference. However, following further consideration of the available evidence, the recommendation for FLI to diagnose NAFLD has been removed due to uncertainties in the evidence base, and a high priority research recommendation has been written in its place to further inform the evidence base. Ultrasound was the next most cost-effective test in adults and the GDG agreed it was widely accepted as an appropriate diagnostic tool for children and young people as there was no clinical reason to believe that the performance would differ in a younger population. The GDG therefore recommended that ultrasound should be used as the preferred diagnostic test for NAFLD in children and young people at highest-risk (those with diabetes or metabolic syndrome).
Perspectum Diagnostics Ltd	Short	4-5	21-25; 1-13	See comment 10 (ID53) in re: full guidelines (p16, line 1-14)	Thank you for your comment. The GDG extensively discussed the available evidence for all of the non-invasive tests listed in the review protocol (Appendix C), including the quality of the evidence and these discussions are captured in the 'Recommendations and link to evidence' section 7.6 in the full guideline. With respect to the reference you provided (Rosenberg 2004) the accuracy figures you mention (based we presume on the figures in row 2 in Table 2 in the full guideline) are in relation to the performance of ELF in the whole cohort of patients with diverse chronic liver diseases (n=921 with adequate biopsy). As you will note in the protocol for the review question in this guideline (detailed in Appendix C in the full appendices), the population of interest was adults, children and young people already diagnosed with NAFLD. Table 5 in the full guideline of the Rosenberg 2004 paper lists the performance of ELF at different thresholds to detect advanced fibrosis (F3 and above) in a NAFLD specific population. This shows much higher accuracy (89% sensitivity and 96% specificity at a threshold of 0.375, and 78% sensitivity and 98% specificity at a threshold of 0.462). While this paper provides insufficient evidence for inclusion in the systematic review and diagnostic meta-analysis conducted for this review question, the reported performance is in line with the available evidence when looking at the population specified in the review protocol.
Perspectum Diagnostics Ltd	Short	9	29	This statement implies that invasive biopsy is the only method for identifying people with NASH. It is more accurate to say that it is the only agreed standardised method for diagnosis of NASH.	Thank you for your comment. We do not feel any amendment is necessary.
Perspectum Diagnostics Ltd	Appendices	601	-	The above highlighted publication by Banjeree et al. 2014 provides evidence for use of multiparametric MRI as an appropriate non-invasive diagnostic tests for the identification of NASH or any level of fibrosis. Inclusion of this study would permit modelling the progression of NAFLD with greater specificity, not limited to advanced fibrosis (F3) only.	Thank you for your comment. Banerjee 2014 was identified as a potential publication for inclusion but on closer inspection of the full paper it was excluded from the review on the basis that the population identified with steatohepatitis included those with both alcohol-related and non-alcoholic liver disease. Although the authors provided some information about identifying steatosis in a subgroup analysis of those with NAFLD (page 73 and supplementary figure 6 in the full guideline) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there was insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool.
Perspectum Diagnostics Ltd	Appendices	643	29-42	The conclusion from this economic modelling is that testing for NAFLD is cost-effective vs. no testing (at threshold of £20,000 per QALY) with a retesting frequency of 5 years being most effective. While the FLI (fatty liver index) ranked first in terms of Net Monetary Benefit (NMB), we note there is very little between the 10 strategies evaluated.	Thank you for your comment. We agree that there was relatively little difference between some of the alternative testing strategies, although FLI clearly came first. The section you refer to is an evidence statement, which follows a set style for consistency, and so it would not be appropriate to add additional comments here. It is however clear in the full results in

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				This should be explicitly stated in the summary.	Appendix N that the results for several of the strategies were close, and this has also now been added more explicitly in the summary of the model in section 6.4.3 of the full guideline.
Perspectum Diagnostics Ltd	Appendices	644	4-22	The conclusion from this economic modelling is that testing adults with NAFLD for advanced fibrosis was cost effective vs. no testing (at threshold of £20,000 per QALY) with a retest frequency of 3 years being most effective. While the ELF test ranked first in terms of Net Monetary Benefit (NMB), we note there is very little difference between the 15 strategies evaluated. This should be explicitly stated in the summary.	Thank you for your comment. We agree that there was relatively little difference between some of the alternative testing strategies, although ELF and the 2-stage tests were clearly preferable to the other alternatives. The section you refer to is an evidence statement, which follows a set style for consistency, and so it would not be appropriate to add additional comments here. It is however clear in the full results in Appendix N that the results for several of the strategies were close, and this has also now been added more explicitly in the summary of the model in section 7.4.3 of the full guideline.
Perspectum Diagnostics Ltd	General	-	-	Formatting: There are some inconsistencies in the table formatting and level of detailed captured in each table of the clinical evidence included in each review chapter. For example, population n's are missing from Table 24 and Table 40, but included in Table 8 and 18. Also the page numbers appear to have been clipped off the bottom of each page.	Thank you for your comment. These have been corrected.
Department of Health				Thank you for the opportunity to comment on the draft for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you.
British Association for the Study of the Liver (BASL)	General			In many cases NAFLD is part cause of liver disease. There is no clear indication, with the exception of alcohol related liver disease, that NAFLD is an important co-factor in progressive liver injury where NAFLD is not the primary cause of fibrosis, nor appreciation that where there is mixed aetiology that the effects of NAFLD may be more severe. Thus the guideline regarding NAFLD should also be directed at patients with other aetiologies who also happen to have NAFLD. Alcohol related liver disease is but one example.	Thank you for your comment. We acknowledge that people with NAFLD may have other coexisting liver injury however management of mixed aetiology was not prioritised for this guideline. Detail has been added to the introduction in chapter 2 in the full guideline to make this clear.
British Association for the Study of the Liver (BASL)	General			NAFLD can arise in a patient who has a high BMI but does not have type-2 diabetes mellitus nor has insulin resistance. Such a patient may be at future risk of those conditions. It is appreciated that central obesity is considered part of the n]metabolic syndrome but it might be better if this was explicit.	Thank you for your comment. People with high BMI but not diabetes were considered in the clinical evidence review (chapter 5 in the full guideline) and health economic model (Appendix N in the full appendices). A definition of metabolic syndrome has now been added to the glossary.
British Association for the Study of the Liver (BASL)	General			Liver disease of all aetiologies can be present in those with normal Liver function tests.	Thank you for your comment.
British Association for the Study of the Liver (BASL)	Full	78		The evidence supporting the use of the fatty liver index was not considered robust. Another view was that using the fatty liver index to screen would identify very large numbers of patients that might exceed capacity.	Thank you for your comment. The GDG extensively discussed the available evidence, including the quality and these discussions are captured in the 'Recommendations and link to evidence' section 6.6 in the full guideline, as detailed in the boxes on the trade-off between clinical benefits and harms, the trade-off between net clinical effects and costs, and the quality of the evidence. Following further discussion, due to variation in the cost-effectiveness results for all tests under certain scenarios and uncertainty in the underlying evidence base (FLI diagnostic accuracy), testing for NAFLD was not recommended by the GDG and a high priority research recommendation has been written in its place.
British Association for the Study of the Liver (BASL)	Full	169		The evidence to support the use of probiotics was considered weak and based on small numbers that did not justify the case made.	Thank you for your comment. This has been considered and the GDG has agreed to remove the recommendation. The research recommendation remains in the guideline to highlight that further research is required for probiotics as a treatment for NAFLD.

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British Association for the Study of the Liver (BASL)	Full	288		There was a strong view that ELF was not considered the best test for fibrosis and that it would be hard to justify this on cost effective grounds. The test is expensive and introduction in large numbers to primary care could be very hard to support.	Thank you for your comment. The GDG extensively discussed the available evidence, including the quality and these discussions are captured in the 'Recommendations and link to evidence' section 7.6 in the full guideline, as detailed in the boxes on the trade-off between clinical benefits and harms, the trade-off between net clinical effects and costs, and the quality of the evidence. Based on stakeholder feedback and drawing from the available evidence, the cost-utility analysis was updated to investigate combining the ELF test with dual threshold tests, However, due to a decrease in the cost of the ELF test, which was also incorporated into the updated modelling, ELF remained the most cost-effective (as well as the most diagnostically accurate) test for advanced fibrosis and so the GDG agreed that this ELF should continue to be the recommended test. However, we have acknowledged that the evidence informing the ELF recommendation is not high quality and therefore the recommendation has been reworded to 'consider ELF' to reflect the lower quality evidence.
British Society of Gastroenterology and Royal College of Physicians	Full	78		It is of great concern that the fatty liver index is recommended over ultrasound for testing adults for NAFLD. This is a recommendation that will change current clinical practice and as such it should be based on robust evidence and cost-effectiveness analysis. Nevertheless, the evidence on FLI is of low (or extremely low) quality. There are just three studies on FLI that were considered and only one used the cut-off proposed by the GDG. The FLI was initially developed using ultrasound as the reference standard and had a moderate accuracy of 0.84 (Bedogni 2006). The analysis does also not take into account that US pick up signs of cirrhosis and portal hypertension and focal lesions that could be related to NAFLD and chronic liver disease. It is mentioned that FLI is more available than ultrasound, however it still requires fasting triglycerides which is not readily available in most screening settings. Also the evidence that populated the economic models is of low quality and high uncertainty due to the lack of adequate long-term data of asymptomatic patients with NAFLD at primary care level. Even if one assumes that the modelling is robust (which is not) the difference in QALYs between FLI and US is minimal and certainly not enough to dictate a change in current clinical practice. It is our strong view that US should be the preferred method of screening in eligible patients.	Thank you for your comment. While we agree that the evidence for FLI was of low quality we wish to point out that the evidence for ultrasound was of very low quality. As can be seen in the review protocol in Appendix C in the full appendices, only studies that compared the index test to liver biopsy as a reference standard were included in this review. As described in the section 'Recommendations and link to evidence' in the full guideline, the GDG explored the robustness of the original economic analysis by conducting extensive sensitivity analysis. This examined the uncertainty attached to the clinical evidence in the model. However, it is clear that ultrasound is considerably more expensive than FLI. Therefore, despite the fact that it may have better diagnostic accuracy, it is very unlikely that using ultrasound for diagnosis of NAFLD could rank higher in terms of cost-effectiveness compared to FLI. The GDG agreed that when NAFLD is currently tested for then ultrasound is the most commonly used tool. However, current standard practice is not to test for NAFLD at all in the vast majority of people at risk of NAFLD, and so even those receiving ultrasound are relatively a very small group. The GDG noted that ultrasound can give additional information as well being used to assess for presence or absence of NAFLD. Although this could not be quantified, the GDG took this into account in making its recommendation. Due to variation in the cost-effectiveness results for all tests under certain scenarios and uncertainty in the underlying evidence base (FLI diagnostic accuracy), testing for NAFLD was not recommended by the GDG and a high priority research recommendation has been written in place of this recommendation. People who have additional symptoms or blood test results indicating that ultrasound may be beneficial for additional reasons other than merely considering a diagnosis of NAFLD can of course still be referred for an ultrasound based on the clinician's judgment. This may cover a significant proportion of the small number of people suspected for NAFLD currently receiving an ultrasound. However, for the typical patient with type 2 diabetes or metabolic syndrome there is no need for an ultrasound just to diagnose NAFLD.
British Society of Gastroenterology and Royal College of Physicians	Full	109	20	It is a serious methodological flaw that the cut-off of a non-invasive test used in a pediatric population (median age 14) is extrapolated and used for diagnosis and decisions in adults, also taking into account that NASH is a different disease in pediatric populations with distinct distribution of fibrosis. It is very unclear why of all three ELF studies the one by Nobili was selected for the economic modelling and the subsequent	Thank you for your comment. The GDG did not believe there was any indication that the performance of the ELF test would differ in an adult population, as adults with advanced fibrosis have a similar proportion of fibrosis but differently distributed. The Nobili study was chosen due to the higher quality of the evidence (low compared to very low).

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				recommendation. There is a serious spectrum bias in the study as just 8/112 subjects had F3/4 fibrosis and the majority (95) had no or minimal fibrosis. Therefore the diagnostic accuracy of the ELF test is most probably inflated. It also makes no sense to note that both sensitivity and specificity rise as the threshold increases. An independent dataset should demonstrate decreased sensitivity as the threshold rises. Accordingly the proposed cut-off would likely lead to massive under-diagnosis of advanced disease in adult populations. ELF is not liver specific and can lead to false positive results in adult populations due to fibrotic processes in other organs, hence the reduced diagnostic accuracy in adults with NAFLD (Guhas 2008). It is therefore no surprise that it is considerably influenced by age (Lichtingagen J Hepatol 2013). We strongly suggest for the analysis of the Guha study instead with revised sensitivity and specificity.	Following stakeholder consultation this recommendation has been amended to: consider using ELF to test people for advanced fibrosis. The addition of the word 'consider' reflects the uncertainty in the evidence. While we agree (and mention in other sections of the guideline) that an increase in sensitivity will consequently reduce specificity, and that this pattern is not present in the table of ELF accuracy ratings, we believe this is due to the small number of studies (3) with different population sizes. The same lack of expected pattern is visible in the data from papers on FIB4, NAFLD fibrosis score and transient elastography where we have different sizes of studies across the different thresholds.
British Society of Gastroenterology and Royal College of Physicians	Full	109	22	It is not clear why only the low cut-off of FIB-4 is analysed. The FIB-4 is designed as a dual cut-off test – low cut-off to rule out advanced fibrosis and high cut-off to rule in advanced fibrosis. A number of patients fall in the grey zone and need re-testing. Any robust economic modelling should have included a two-tier testing, with ELF or Fibroscan or ARFI or MR elastography in patients in the grey zone of FIB4 or NAFLD fibrosis score (Crossan Health Technology Assessment 2015).	Thank you for your comment. Following the consultation we have amended the original economic analysis to add in 2-stage tests as additional options for diagnosing advanced fibrosis – specifically using either FIB-4 or NAFLD fibrosis score as the initial test using both high and low thresholds to rule in and rule out fibrosis, followed by either ELF or ARFI for those with indeterminate results in the first test. Though these 2-stage tests performed well in the economic analysis (second to fifth places), ELF (with a reduced cost due to new cost information) again ranked in first place in the analysis. However, we have acknowledged that the evidence informing the ELF recommendation is not high quality and therefore the recommendation has been reworded to 'consider ELF' to reflect the lower quality evidence.
British Society of Gastroenterology and Royal College of Physicians	Full	110	3	As above, it is unclear why only the high cut-off of NAFLD fibrosis score is analysed in the economic modelling. This is a dual cut-off test and should be treated as such.	Thank you for your comment. Following the consultation we have amended the original economic analysis to add in 2-stage tests as additional options for diagnosing advanced fibrosis – specifically using either FIB-4 or NAFLD fibrosis score as the initial test using both high and low thresholds to rule in and rule out fibrosis, followed by either ELF or ARFI for those with indeterminate results in the first test. Though these 2-stage tests performed well in the economic analysis (second to fifth places), ELF (with a reduced cost due to new cost information) again ranked in first place in the analysis. However, we have acknowledged that the evidence informing the ELF recommendation is not high quality and therefore the recommendation has been reworded to 'consider ELF' to reflect the lower quality evidence.
British Society of Gastroenterology and Royal College of Physicians	Full	110	4	It is unclear why this specific TE cut-off of the M probe was selected with suboptimal diagnostic accuracy. At least two further cut-off of the M probe should be tested in the economic modelling. There are cut-offs that performed equally well to the ELF cut-offs therefore a serious source of bias is inserted in the economic modelling by selecting the best performing cut-off of a non-invasive test versus a less optimal one of another.	Thank you for your comment. The cut off range of 7.8-7.9 was selected by the GDG for use in the economic model because evidence for this threshold was based on pooled diagnostic meta-analysis data from multiple studies, and so was preferred over those thresholds that only had evidence from single studies. So while some higher thresholds suggested better performance (for example, 10.2 and 10.4) these thresholds contained information only from single studies with small sample sizes (n<100). The threshold chosen by the GDG had pooled data from n=522 and the highest sensitivity of the thresholds where it was possible to conduct diagnostic meta-analysis.
British Society of Gastroenterology and Royal College of Physicians	Full	116	5	The recommendation of ELF as first line testing for all patients diagnosed with NAFLD is based on flawed evidence (comment 2 (ID91)) and has serious practical and financial implications. At the moment, there are two simple and readily available non-invasive tests (namely FIB-4 and NAFLD fibrosis score) that have optimal negative likelihood ratios at their low cut-offs that would automatically rule out 50% of patients with NAFLD from further testing. This approach would be much more practical (as these simple tests are available at the point of care) and would save the NHS a lot of money, For those patients with values above the low cut-off, a second tier testing would be required. We strongly suggest that this should be based on local availability rather than a recommendation of ELF above all other tests. There is no direct evidence of the	Thank you for your comment. Following the consultation we have amended the original economic analysis to add in 2-stage tests as additional options for diagnosing advanced fibrosis – specifically using either FIB-4 or NAFLD fibrosis score as the initial test using both high and low thresholds to rule in and rule out fibrosis, followed by either ELF or ARFI for those with indeterminate results in the first test. Though these 2-stage tests performed well in the economic analysis (second to fifth places), ELF (with a reduced cost due to new cost information) again ranked in first place in the analysis. However, we have acknowledged that the evidence informing the ELF recommendation is not high quality and therefore the recommendation has been reworded

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				superiority of ELF over Fibroscan, ARFI or MR elastography. There is limited data on ELF that have not been independently validated in other groups. The economic modelling should test the two-tier approach.	to 'consider ELF' to reflect the lower quality evidence.
British Society of Gastroenterology and Royal College of Physicians	Appendix N			The data used to populate the Markov models for the economic analysis are of low quality due to inadequate long-term data in patients with NAFLD. This is a serious flaw and should be reflected in the strengths of the recommendations. It also appears from the model that universally all patients with NAFLD will progress to more advanced liver disease, which is certainly not the case and could over-estimate the disease burden.	Thank you for your comment. The economic model was built probabilistically to take account of the uncertainty around input parameter point estimates. Long term progression data were sourced from a recent meta-analysis with a paired biopsy design. This took into account the proportion of patients that have not progressed during the median study follow up (62 months). Due to variation in the cost-effectiveness results for all tests under certain scenarios and uncertainty in the underlying evidence base (FLI diagnostic accuracy), testing for NAFLD was not recommended by the GDG and a high priority research recommendation has been written. In the model all patients are on a liver disease pathway which includes advanced liver disease such as cirrhosis, but not all individuals will reach cirrhosis, since some will improve following treatment and others will remain in the states representing steatosis or advanced fibrosis until their deaths without any further progression.
British Society of Gastroenterology and Royal College of Physicians	Full	169	14	It is our strong recommendation that the section on explaining the potential role of probiotics to adult patients should be removed. There are three very small studies of less than 12 months follow up and with 100 patients in total that used very soft and non-validated end points such as transaminases, spectroscopy and elastography. This evidence is very preliminary and should be tested in adequately powered phase II and III studies with sufficient duration and commonly accepted histological endpoints. Until such studies are performed, this statement has no place as a NICE recommendation. Indeed the data on coffee are much stronger however there is no recommendation on coffee.	Thank you for your comment. Following stakeholder consultation we have removed the recommendations relating to probiotics from the guideline.
British Society of Gastroenterology and Royal College of Physicians	Full	288	17	There is absolutely no evidence that ELF (or any other noni-invasive test) can be used to monitor the response to medical treatment for NAFLD. Existing evidence suggests the use of liver histology. If a recommendation on non-invasive testing is made, then there is no proven superiority of ELF over Fibroscan, ARFI or MR elastography.	Thank you for your comment. The objective of the monitoring review was to discover progression rates of NAFLD and subsequently who (in terms of severity of disease) should be monitored for progression and how often. We did not conduct a review on the most clinically and cost-effective tests to monitor response to pharmacological treatments for advanced fibrosis. Therefore, as discussed in the 'other considerations' section of 17.6 'Recommendations and link to evidence' in the full guideline, the GDG felt that it was the most logical and appropriate compromise to assess treatment response (to allow re-evaluation about whether the benefits of continuing therapy still outweighed potential risks) using the same non-invasive means recommended for identifying advanced fibrosis. The GDG believed that since severe hepatic fibrosis has consistently been shown to be of prognostic value in people with NAFLD, these people require closest monitoring and have the most to gain from pharmacotherapy to slow or reverse the progression of fibrosis.
British Society of Gastroenterology and Royal College of Physicians	Full			Many of the recommendations are based on studies that have been evaluated as at high risk of bias or of low quality. This really needs to be made clear. Similarly the difference in economic calculations that support some of the selections – in the present form all recommendation are given the same weight with no signposting on the quality of evidence that supports these recommendations.	Thank you for your comment. The GRADE rated quality (which takes into account the risk of bias amongst other factors) for each outcome has been clearly stated in all clinical evidence summary tables, in the evidence statements and summaries in the 'Recommendations and link to evidence' tables. It is NICE policy not to give recommendations a numerical or letter rating, instead the strength of the evidence is reflected in the wording of the recommendation, in line with the NICE guidelines manual. (For example, recommendations saying 'Consider…' are weaker than recommendations saying 'Offer…').
British Society of Gastroenterology and Royal College of Physicians	Full			It is very contentious to only refer patients with advanced fibrosis (F3-F4) to an hepatologist. Opportunities for earlier interventions might be missed in patients with NASH and comorbidities who are at risk of progression. These individuals would also miss the opportunity to participate in clinical trials, which invariably rule out patients with cirrhosis.	Thank you for your comment. As discussed in chapter 7 on diagnosing severity of NAFLD in the full guideline, the evidence for diagnosing NASH demonstrated limited efficacy and no test could be recommended. As there is currently no cost-effective way to reliably identify those with NASH, it is not possible to recommend those with NASH be referred to a hepatologist. The GDG agrees that it is important to identify these people and made a high

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					priority research recommendation to identify the most accurate non-invasive test to diagnose NASH in all ages. There is no reason why trials cannot recruit people from primary care. The guideline does not preclude referral for non-routine reasons, but the GDG does not believe it would be necessary or cost-effective to refer everyone with NAFLD as there is little that hepatologists could add beyond primary care. Liver-related mortality is much smaller for those with less advanced fibrosis (F0–F2), regardless of presence or absence of NASH, and recent studies show that it is the presence of advanced fibrosis (F3–F4) that determines long-term prognosis, such that requires specialist hepatologist-led management.
British Society of Gastroenterology and Royal College of Physicians	Full	62		The GDG prioritized the testing of patients with metabolic syndrome or type II diabetes over that of obesity, high triglycerides and low HDL levels despite all of the above being cost-effective. There is no mention in the testing of patients with abnormal LFTs and metabolic abnormalities other than type II diabetes and metabolic syndrome. It is clear that normal transaminases should not preclude testing, however abnormal transaminases should prompt further investigations in primary care. Should such individuals not be further investigated for fatty liver? It does not make sense to screen an asymptomatic lean patient with type II diabetes with normal LFTs at his sixties and not test a 45 year old individual with a BMI of 45, abnormal LFTs and high triglycerides (who does not however fulfil the 3/5 criteria for metabolic syndrome).	Thank you for your comment. Chapter 5 in the full guideline assessed the clinical evidence for waist circumference, BMI, raised triglycerides, low HDL-cholesterol, type 2 diabetes, hypertension, age and metabolic syndrome as possible risk factors for NAFLD. The GDG agreed that of those risk factors that were included in the model, type 2 diabetes and metabolic syndrome had the largest effect and the results were the most clinically significant. The GDG agreed that the clinical evidence for other risk factors was weaker. In addition, the original economic analysis showed that, although testing was cost-effective compared to no testing for all risk factors considered at base case assumptions, it was most cost-effective for people with type 2 diabetes or metabolic syndrome. The GDG thus chose to concentrate on these 2 groups. No data were available for populations with combinations of multiple risk factors (other than metabolic syndrome, which is itself a combination of risk factors), and so the cost-effectiveness of such populations could not be assessed. Whilst the GDG accepts that there will always be exceptional cases, it does not believe that the 2 hypothetical patients proposed are likely scenarios.
British Society of Gastroenterology and Royal College of Physicians	Full	60		A study on the risk factors of NAFLD in the UK by Alazawi (2014;64:694-702) was missed from the search strategy (not mentioned in the excluded studies in appendix N either)	Thank you for your comment. Alazawi 2014 would not be included in the evidence review looking at risk factors for NAFLD as it focusses on ethnicity as a risk factor, which the GDG did not prioritise as a risk factor for this protocol as it was noted that it is already established that the prevalence of NAFLD is higher in people of Latin American and South Asian family origin. Furthermore, this study has a cross-sectional design and would also have been excluded on this basis. It was excluded at the initial sifting stage for these reasons and therefore does not appear in the excluded study lists.
Royal College of General Practitioners	Full	General	General	This guideline is essentially for screening patients with type 2 diabetes or metabolic syndrome for NAFLD, but has not been looked at by the National Screening Committee. It fails on most of Wilson's criteria for a screening programme. Most patients with NAFLD will never have any symptoms at all from it or progress to symptomatic fibrosis. The treatments consist of the same lifestyle changes that would be offered to this group of patients anyway. The tests are expensive and the ELF is not currently available in most centres. It is completely unresourced, and would currently be impossible to deliver in general practice or the UK generally without a major and inappropriate diversion of funds from elsewhere in the NHS. (JS)	Thank you for your comment. This recommendation was not for a national population screening programme, and so this does not fall under the remit of the National Screening Committee. The guideline informs identifying people at high risk of NAFLD (diabetes and metabolic syndrome as identified in the risk factor review in chapter 5 in the full guideline) to consequently prevent progression to more severe disease. Following further discussion, the recommendation for targeted case finding using FLI has been removed due to uncertainties in the evidence base, and a research recommendation has been written to inform future updates of the guideline. The GDG discussed in depth the symptoms and progression of NAFLD. Based on the severity review in chapter 7, no test was found to be sufficient for diagnosing NASH or F0–F2 fibrosis. Consideration of this evidence alongside the GDG's clinical expertise and experience that it is the presence of advanced fibrosis (F3–F4) that determines long term

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					prognosis, the GDG made recommendations for identifying those with NAFLD and advanced fibrosis (F3 or above). The treatments for people with NAFLD include lifestyle management programmes that could currently be offered to many of those in this group, but regrettably have a low level of take-up, which we hope this guideline will help to improve. However, this guideline also includes recommendations on regular monitoring for progression to advanced fibrosis and then cirrhosis, and pharmacological treatment using pioglitazone or vitamin E for those with advanced fibrosis. Further treatment for those with NAFLD and cirrhosis is covered in the NICE cirrhosis guideline. The cost of ELF has reduced, and this has been amended following consultation in the final version of this guideline. It is now slightly cheaper than an ultrasound or other imaging test, and is the most cost-effective test for advanced fibrosis at a cost-effectiveness threshold of £20,000 per QALY gained, as well as the most diagnostically accurate. ELF is available on request from laboratories, but is currently infrequently used in most of the country. CCGs in some areas, which have already adopted a testing strategy involving ELF, already use ELF routinely. While there will be upfront implementation costs, ELF was the most clinically and cost-effective test and as such is a cost-effective use of NHS resources compared to spending in all areas of the NHS. The GDG works with the cost implementation team at NICE to help plan implementation support based on the recommendations following publication of the guideline.
Royal College of General Practitioners	Full	General	General	The major problem with this guideline is the assumption that NAFLD is indeed a disease, which it isn't. If it were considered a risk factor for cirrhosis then the approach of the enquiry would be completely different. The rational approach would then be to consider the diagnosis of NAFL as a screening programme to prevent death from cirrhosis. The problem here, as will be detailed below, is that there is no recognised treatment to prevent cirrhosis, and it is therefore impossible to assess the success or otherwise of the whole approach. For that reason I was intrigued with the economic analyses. With no clear benefits in terms of lives saves or quality of life improved how can the cost per QALY be calculated? There is the additional problem that the risks cannot be quantified for patients' benefits. If BP as a risk factor for ischaemic heart disease is used as a comparison, we are now able to discuss with patients the likely benefits and risks of treating or not treating. Here there is no clue given as to the long term risks in numerical terms of someone with NAFL developing cirrhosis. A moment's reflection indicates why this is important: a 5% lifetime risk would be laughed off by many, but not all; a 50% lifetime risk would be taken seriously by most. The overall recommendation that all patients with type 2 diabetes should be tested is little short of preposterious. (DJ)	Thank you for your comment. Whilst the GDG affirms that NAFLD is indeed a disease, it is happy to also agree that it is a risk factor for cirrhosis. The approach taken in this guideline, and in particular in the economic modelling in Appendix N in the full appendices, is to follow up a diagnosis of NAFLD both by treating people with NAFLD, and by monitoring them for progression to cirrhosis. The treatment stage includes lifestyle modification for people with NAFLD, and the option of pharmacological treatment for people with NAFLD and advanced fibrosis, both of which have been shown to reduce or reverse progression of liver disease, thereby reducing the number of people who would ultimately progress to cirrhosis. If and when people with NAFLD do reach the stage of cirrhosis they would then receive interventions as recommended in the NICE Cirrhosis guideline (monitoring for varices and monitoring for hepatocellular carcinoma), which have been shown to reduce mortality in people with cirrhosis. The overall effect of these interventions, when modelled, was to avert deaths and gain life years and QALYs. Testing for NAFLD was consequently found to be cost-effective for people with type 2 diabetes or metabolic syndrome. The risks of NAFLD and the benefits of testing can be quantified (acknowledging that there are clearly margins of uncertainty) – various outcome measures, such as risk of dying from a liver-related cause, are presented in the full results in Appendix N in the full appendices. However, following further discussion regarding the uncertainties of the evidence base, the recommendation for targeted case-finding has been removed and a high priority research recommendation has been written to inform future updates of the guideline.
Royal College of General Practitioners	Full	General	General	It would be helpful to have a detailed breakdown of the epidemiology and changing pattern of disease.. There is no comment on Vaccination with Hep A and B which would be important in	Thank you for your comment. This guideline includes a short introduction but can only contain so much detail as to help set the context for the specific topics prioritised for review questions. It cannot provide the level of detail that might be expected in a textbook on liver

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				preventing liver damage from virus infections in a liver already at risk. (PS)	disease (i.e. detailed breakdowns of the epidemiology of different liver-related diseases and pattern(s) of progression). The introduction has been updated to provide references that can be sought out for more detail specific to NAFLD. With respect to the topic of vaccination for hepatitis A and B we would refer you to the introduction to the full guideline in chapter 2. We have added more detail to highlight that while the GDG acknowledges that some people with NAFLD may also have an additional aetiology of liver disease, this was not included in the scope and therefore a review question for this specific topic was not conducted.
Royal College of General Practitioners	Full	General	General	The document states that results of the original economic model demonstrated that FLI was the most cost-effective test to use to diagnose NAFLD in adults who had type 2 diabetes or metabolic syndrome. NICE needs to take more ownership of the practicalities of implementation in general especially to non-specialist audiences ie primary care - and hence to factor in more of the costs of achieving change in the initial modelling. It is in adequate to simply consider that these more complex considerations that overlap other aspects of care are outside the scope of the guideline. As things stand, the snap-shot view from a GP perspective is screening DM populations for a new condition - the testing facilities of which are not locally available and for which the primary care workload is completely unfunded. Bearing in mind there is a strong perception that QOF is on its way out, the issue of how this diagnostic work might be funded is of high relevance. There is deepening crisis for general practice, unsustainable workloads, exhausted GPs and local practices closing down by the dozen because there is no one left to run them. There are patient safety implications of excessive workload and fatigue in general practice received an overwhelming response from GPs for whom very high levels of stress and tiredness are a fact of daily life. In 2015, 72 practices were forced to close their doors, forcing more than 200,000 patients to register elsewhere – a huge leap from the previous year. GPs and our teams are making in excess of 370m patient consultations a year to keep up with the demand of our growing and ageing population. There are 60m more consultations than five years ago, yet funding for general practice has declined dramatically in real terms over the last ten years, and our workforce has remained stagnant. In the Midlands alone a study recently commissioned by the RCGP's Midland Faculty found that 82% of GPs said they intend to leave general practice, take a career break and/or reduce their clinical hours of work within the next five years. (MH)	Thank you for your comment. The economic modelling in Appendix N in the full appendices was conducted to assess the cost-effectiveness per person of diagnostic testing as part of an ongoing testing programme, in line with standard NICE practice. Therefore, initial start-up costs were not included in the health economic modelling. NAFLD is an already widespread disease for those at high risk and who have not previously been monitored systematically. FLI is a simple calculation and is freely available online. In similar cases where NICE has recommended the use of specific formulae these have subsequently been rapidly integrated into primary care record management systems. No testing facilities are needed other than for triglycerides and GGT, which are already common blood tests. NICE compares all proposed interventions to the same common standard of cost-effectiveness to ensure that recommendations are made fairly in the interests of the effectiveness and efficiency of the health service as a whole. We find that carrying out testing is cost-effective, therefore it is appropriate to recommend such testing and for the NHS to spend money on it.
Royal College of General Practitioners	Full	General	General	There are difficulties of recommending a test that is simply not available to general practice. ie FLI requires some sort of calculation to interpret BMI waist circ, trigly and gamma GT. This is not on EMIS etc ELF requires interpretation of some blood test biomarkers using a patented Siemens proforma. This is not yet commonly available and would need to be commissioned before GPs could use it. (MH)	Thank you for your comment. Following further discussion regarding the uncertainty in the evidence base the recommendation for FLI has been removed. ELF is already available and can be processed by laboratories, though it has previously been rarely requested.
British Liver Trust	Full	General	General	There does not appear to be any recognition of 'low platelet count' as a possible indicator of NAFLD. My consultant hepatologist confirms that he often has referrals where the only indicator is low platelet count. This was my experience. I am a recent recipient of a liver transplant. I was only diagnosed with NAFLD, NASH and HCC. Although a little overweight since childhood, I've never abused alcohol and abstained completely for most of my life. Except for a low platelet count (first noticed in 2002) all my Liver Function Test were always normal, right up to May 2014, as was my blood/sugar, cholesterol, heart rate and blood pressure. I was always fit and active and very seldom unwell, let alone ill. In January 2014, my platelet count had dropped to	Thank you for your comment. When developing review protocol for the risk factors of NAFLD, the GDG discussed and prioritised the risk factors that were most commonly related to NAFLD. Low platelet counts are recognised as a feature for cirrhosis and hypersplenism but not as an independent risk factor. Therefore, this was not included in the review protocol.

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				about 60 which, while not dangerous, was quite low, so my GP referred me to a haematologist. I had many tests over a period of 4 months and eventually, almost as an afterthought, the haematologist called for a CT scan of my liver. Only then did it come to light that I had NAFLD/NASH which was effectively killing off my platelets resulting in a low count. Also the NASH had put me at much greater risk of the HCC which was quite virulent and, by the time of the diagnosis, almost too large for me to be put on the transplant waiting list. If the connection between low platelets and NAFLD had been made earlier then I could have been diagnosed much earlier, NASH might have been avoided, I probably would not have got cancer and not needed a liver transplant.	
Royal College of General Practitioners	Full	15	12	Since it has been estimated that around 25% of the population have type 2 diabetes or General Practitioners General Practitioners the metabolic syndrome, this is a proposal to screen about a quarter of the UK population using the FLI which requires clinical measurements and blood testing. Presumably general practice will be expected to undertake the bulk of this work which without significant extra funding which is unlikely to available will not be possible. (JS)	Thank you for your comment. The recommendation for targeted case-finding has been removed following further discussion regarding the uncertainty in the evidence base, and a high priority research recommendation has been added to inform future updates of the guideline.
Royal College of General Practitioners	Full	16	2	Since it has been estimated that up to 75% of the population to be screened has NAFLD then again this a huge number of people to test further using the ELF which is expensive and not available in the majority of hospitals in the UK. (JS)	Thank you for your comment. According to data sources used in the economic model, NAFLD prevalence in people with type 2 diabetes or metabolic syndrome is around 53–54%. However, the recommendation for targeted case-finding has been removed following further discussion regarding the uncertainty in the evidence base. Furthermore, the cost of ELF has reduced, and this has been amended following consultation in the final version of this guideline. It is now slightly cheaper than an ultrasound or other imaging test, and is the most cost-effective test for advanced fibrosis at a cost-effectiveness threshold of £20,000 per QALY gained, as well as the most diagnostically accurate. ELF is already available and can be processed by laboratories, though it has previously been rarely requested.
Royal College of General Practitioners	Full	16	25-32	I note that the only treatment for the majority consists of lifestyle changes which are what would be promoted to the screened group of type 2 diabetes and metabolic syndrome in any case. (JS)	Thank you for your comment. As detailed in section 13.6 'Recommendations and link to evidence' in the full guideline, trade-off between clinical benefits and harms, the GDG was aware that lifestyle interventions may already be being offered to many people with NAFLD as they are likely to also have obesity or diabetes. However the GDG also noted that in addition to the benefits that these interventions provide in terms of weight loss and reduced risk of cardiovascular disease, there is also evidence that they provide the additional benefit of reducing the rate of NAFLD progression. Therefore those people with diabetes or metabolic syndrome as well as NAFLD will get a specific benefit from being referred to lifestyle modification programmes, and a recommendation highlighting this was justified. The GDG noted that lifestyle management programmes currently have a low level of take-up in people with obesity, but consider that this additional evidence and recommendation will help to improve this as anecdotal evidence suggests that diagnosis with more than one condition may increase people's willingness to adhere to lifestyle modifications. In addition to lifestyle changes, this guideline also includes recommendations on regular monitoring for progression to advanced fibrosis and then cirrhosis, and pharmacological treatment using pioglitazone or vitamin E for those with advanced fibrosis. (Further treatment for those with NAFLD and cirrhosis is covered in the NICE cirrhosis guideline).
Royal College of General Practitioners	Full	18	8	There are no plans to look at things that individuals can do such as dietary changes. Does a high carb/low fat diet work? Does a low carb/healthy fat diet work? There is some evidence that latter improves NAFLD before weight falls that much, and some consideration of uncertainty around this would be useful as it allows exploration of	Thank you for your comment. Dietary interventions have been considered in this guideline in several evidence reviews. Chapter 10 of the full guideline is focussed on weight loss which involves many forms of dietary interventions that is, very low calorie diet and calorie restriction (low fat, low carbohydrate, high protein, percentage fat, percentage carbohydrate, percentage protein). However no evidence matching the review protocol was identified for

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				what works for an individual. For example, a milk diet is used prior to bariatric surgery to reduce liver fat. Developing this intervention to a long term sustainable diet may be useful for NAFLD. it is disappointing that there is a dearth of treatment options discussed, and as there is very little in a medical model, it is the bio-psycho-social approach that is our only tool, and this has to include something that is not simply the same old lose weight mantra. It has to be actionable, and we need more research to establish what different approaches to diets might actually work. I suspect this will be low carb, but let's see evidence. (AH)	people with NAFLD. Similarly, Fructose and sugar (sucrose) intake were considered in chapter 15 of the full guideline for people with NAFLD, however no relevant evidence was identified. The GDG did not prioritise these areas for research recommendations as there was doubt over the feasibility of conducting such studies and therefore felt other areas should be prioritised. Chapter 13 in the full guideline looked at lifestyle modification interventions which involved dietary modification, and the recommendation made from this states 'improve eating behaviour and the quality of the person's diet, and reduce energy intake' (Lifestyle intervention recommendation from NICE's obesity guideline).
Royal College of General Practitioners	Full	18	18- 22	Weight loss is primary thing that will help, as does sorting out diabetes - getting sugars under control appears to be critical to treating this in practice. It would be great to see these both more emphasised. This is very likely to be a disease of insulin resistance, and tackling this will aid a return to normal liver. (AH)	Thank you for your comment. The GDG agree that weight loss is a very important aspect of the management of NAFLD. Therefore the GDG recommended weight loss through physical activity and dietary modification as part of lifestyle modification and referred to NICE's obesity guideline for further guidance (please see recommendation 18 on weight reduction). This has been further highlighted in the 'other considerations' section of the 'Recommendations and link to evidence' section of chapter 13 in the full guideline which refers to weight loss having the long-term benefit in reducing NAFLD progression.
Royal College of General Practitioners	Full	19	9	The prevalence of NAFL is quoted as 20% or higher (and repeated elsewhere). This is a surprisingly high figure. Unfortunately it is not referenced so I was not able to check the possibility that there might be a flaw in the study or studies from which it was derived. (DJ)	Thank you for your comment. Appropriate references have been added which provides data on the prevalence of NAFLD and evidence that this is increasing worldwide.
Royal College of General Practitioners	Full	19	14	*'The prevalence of NAFLD is increasing, placing a greater burden on healthcare resources.'* This is highly disingenuous. If the prevalence is increasing then it is possible that it is the result of doctors looking for it more. If it were accepted that it is simply a risk that could be ignored then it would place no additional burden on healthcare resources. (DJ)	Thank you for your comment. Appropriate references have been added which provide data on the prevalence of NAFLD and evidence that this is increasing worldwide. We do not agree that this is a risk that can be ignored as identifying people can prevent progression to more advanced disease.
Royal College of General Practitioners	Full	21	34, 24,15	It bothers that this will mean pressure to prescribe or pressure in people to buy expensive supplements that have little evidence. Much better to look at ways of reducing omega 6, processed foods and empty calories that increase sugar levels - extra-cellular carbs. (AH)	Thank you for your comment. We agree and have removed the recommendation on probiotics from the guideline.
Royal College of General Practitioners	Full	76	4	One of the fundamental problems is set out in Chapter 6, where it is made clear that there are no robust criteria for making the 'diagnosis' in the first place. It will be noted the test that is eventually recommended (FLI) is reported as having specific of 49-87% (depending on the threshold used); in any case this would lead to large numbers of false positive results with consequent large numbers referred for further testing. (DJ)	Thank you for your comment. The GDG believe there are criteria for diagnosing NAFLD and a range of diagnostic tests (as set out in the protocol) may be used to diagnose the disease. Biopsy is the current gold standard for diagnosis, but this review intended to inform on the best non-invasive method. The GDG extensively discussed the available evidence, including the quality and these discussions are captured in the 'Recommendations and link to evidence' section 6.6 in the full guideline, as detailed in the boxes on the trade-off between clinical benefits and harms, the trade-off between net clinical effects and costs, and the quality of the evidence. The most cost-effective test to use to identify NAFLD is the FLI test at a threshold of 60. This threshold was chosen by the GDG as the most appropriate due to higher specificity (87%) and good sensitivity compared with the higher threshold, hence not leading to large numbers of false positives. Further detail of the economic model involved in the original cost-effectiveness analysis for this review (including how false positives are taken into account) is available in Appendix N in the full appendices. However, after further taking into account the uncertainty in the model and specificity of FLI, this recommendation has been removed and a high priority research recommendation has been written to inform this evidence base for future updates of the guideline.
Royal College of General Practitioners	Full	78	6.6	Has there been any discussion of training costs or of specifying a costed incentivisation mechanism for primary care to adopt this new work? (MH)	Thank you for your comment. Planning training is outside of NICE's role, however we anticipate that training would be integrated into regular ongoing professional training.

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					Whether incentivisation mechanisms would be appropriate with regard to this guideline will be considered in future by the relevant authorities. NAFLD has been referred to NICE for a quality standard by the Department of Health.
Royal College of General Practitioners	Full	79	6.6	*'Furthermore, the GDG expressed some concerns about the interpretation of results of these imaging tests; for example, the GDG noted a wide range of practice in the means by which fatty liver is identified by clinicians performing ultrasound, as there is no universally accepted definition on what exactly constitutes a diagnosis of steatosis on ultrasound.'* This statement is not surprising. However if the absence of clear diagnostic criteria is acknowledged why is its influence not taken into account elsewhere in the guideline? (DJ)	Thank you for your comment. We are unsure what specific sections you are referring to when you say 'elsewhere in the guideline'? Ultrasound was included as an index test to be compared against the gold standard of liver biopsy in both the diagnosis and severity reviews as it is widely accepted as an identification tool in both adults and children with NAFLD, however there are reservations in using this tool which have been made. The guideline does not go on to recommend the use of ultrasound to identify NAFLD or advanced fibrosis in adults as it was not the most clinically or cost-effective test. Due to the scarcity of evidence regarding non-invasive tests in children and young people, and a lack of alternatives (as FLI may not be valid in children due to the requirement of a waist circumference measurement) the GDG recommended that ultrasound be the preferred test in the paediatric population. However, the GDG also made a high-priority recommendation for more research on the accuracy of non-invasive tests in children and young people.
Royal College of General Practitioners	Full	81	6.6	Given the diagnosis of type 2 diabetes will not be made until after the age of 58, and that the model predicts that testing after that age will not be cost effective, why is this not reflected in the overall recommendation on p14? (DJ)	Thank you for your comment. Based on the information cited from the type 2 diabetes guideline, we believe the *average* age at diagnosis of type 2 diabetes is just below 58. At 58 years, testing for NAFLD has an ICER of below £20,000 per QALY gained compared to not testing (this is a small decrease from the figure of fractionally over £20,000 quoted in the consultation version of this guideline, as small improvements to the model have since been made and the results recalculated. However, due to variation in the cost-effectiveness results for all tests under certain scenarios (that included changing the starting age to 58 years) and uncertainty in the underlying evidence base (FLI diagnostic accuracy, including the uncertainty in specificity), testing for NAFLD was not recommended by the GDG.
Royal College of General Practitioners	Full	170	11.6	*'…however, the GDG also noted that the magnitude of improvement in outcome measures tended to be so modest that their clinical significance was unclear.'* The possible findings on probiotics were interesting, and there is even an (unreferenced) explanation why they might be effective on p157, para 11.1. However the cautious wording cited here is not reflected in the recommendation under 11.6. (DJ)	Thank you for your comment. Following stakeholder consultation we have removed the recommendations relating to probiotics from the guideline.
Royal College of Pathologists	Both	General	General	I found these guidelines clear, very well evidenced, and a really useful piece of work. Just one comment	Thank you.
Royal College of Pathologists	short	8	12	"A grade of F3 or above using the Kleiner (NASH-CRN) or the SAF score. This is referred to as bridging fibrosis (the presence of fibrosis that reaches from one portal area to another)." I suggest changing this to (the presence of fibrosis linking hepatic veins to portal tracts) In fatty liver disease, the bridging fibrosis links hepatic veins to portal tracts - this is in contrast to the other types of chronic liver disease such as viral hepatitis in which there is portal-to-portal bridging fibrosis, for which the Ishak stage is appropriate, and is one reason for using a different staging system for fatty liver disease.	Thank you for your comment. This has been changed.
Royal College of Nursing				For the Liver disease (non-alcoholic fatty [NAFLD]) guideline, nurses caring for people with liver disease reviewed the proposal and have no comments to submit at this stage.	Thank you.