Assessment and management of Cirrhosis

Consultation on draft guideline - Stakeholder comments table
18th December 2015 – 10th February 2016

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Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Royal College of Paediatrics and Child Health				Thank you for inviting the Royal College of Paediatrics and Child Health to comment on the draft guideline consultation for Cirrhosis. We have not received any responses for this consultation.	Thank you for your comment.
British Society of Gastroenterology	Full	13	22	I am concerned that this recommendation 4 specifies the use of the ELF test to define advanced fibrosis in NAFLD with only reference to NAFLD guidance. In the NAFLD guidance the use of AST:ALT ratio > 1 or a NAFLD score > -1.455 is recommended to define possible advanced fibrosis. The data provided in the NICE appraisal support ELF as the best serum test to define advanced fibrosis in NAFLD. However, since the ELF test has a cost implication to most health providers, the recommendation should explicitly state that the readily available NAFLD score can be used to stratify NAFLD patients for advanced fibrosis.	The choice of test for identifying advanced fibrosis in NAFLD, and the evidence for that decision is explained in the NICE NAFLD guideline and the responses to comments on the consultation for that guideline. The NAFLD guideline (consultation and final versions) did not recommend the use of AST:ALT ratio or NAFLD fibrosis score to diagnose advanced fibrosis. The use of NAFLD fibrosis score to stratify patients before using a subsequent test was considered in the final NAFLD guideline but was not recommended.
British Society of Gastroenterology				**Question 1: Which areas will have the biggest impact on practice and be challenging to implement?** I. Training & implementation of Fibroscan +/- ARFI II. Cost of increased hepatology provision in secondary care (hepatologists & nurses) III. Improved commissioning of hepatology services due to increase in referral rate of patients with either risk of cirrhosis or established diagnosis IV. Improved education in primary care (Global awareness of liver disease and treatment) V. Radiology services to provide for HCC screening on 6 monthly basis for cirrhotic patients with good recall mechanism for regular 6 month surveillance	Thank you for your comment. This information will be passed on to NICE's implementation team.
Royal Cornwall Hospitals NHS Trust	Full	13	22	I am concerned that this recommendation 4 specifies the use of the ELF test to define advanced fibrosis in NAFLD with only reference to NAFLD guidance. In the NAFLD guidance the use of AST:ALT ratio > 1 or a NAFLD score > -1.455 is recommended to define possible advanced fibrosis. The data provided in the NICE appraisal support ELF as the best serum test to define advanced fibrosis in NAFLD. However, since the ELF test has a cost implication to most health providers, the recommendation should explicitly state that the readily available NAFLD score can be used to stratify NAFLD patients for advanced fibrosis.	The choice of test for identifying advanced fibrosis in NAFLD, and the evidence for that decision is explained in the NICE NAFLD guideline and the responses to comments on the consultation for that guideline. The NAFLD guideline (consultation and final versions) did not recommend the use of AST:ALT ratio or NAFLD fibrosis score to diagnose advanced fibrosis. The use of NAFLD fibrosis score to stratify patients before using a subsequent test was considered in the final NAFLD guideline but was not recommended.
Royal Cornwall Hospitals NHS Trust				**Question 1: Which areas will have the biggest impact on practice and be challenging to implement?** VI. Training & implementation of Fibroscan +/- ARFI VII. Cost of increased hepatology provision in secondary care (hepatologists & nurses) VIII. Improved commissioning of hepatology services due to increase in referral rate of patients with either risk of cirrhosis or established diagnosis IX. Improved education in primary care (Global awareness of liver disease and treatment) X. Radiology services to provide for HCC screening on 6 monthly basis for cirrhotic patients with good recall mechanism for regular 6 month surveillance	Thank you for your comment. This information will be passed on to NICE's implementation team.
Royal College of Physicians				We would like to formally endorse the response submitted by the British Society for Gastroenterology.	Thank you for your comment.
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.
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 for your comment.
Gilead Sciences Ltd	Short	3	3 1.1.1	Gilead is pleased to note that the draft guidelines provide GPs with some guidance regarding those patients that may be at higher risk of suffering from cirrhosis; however, to provide further clarity for the end-user (non-specialists	Thank you for your comment. Detail on the risk factors for hepatitis is outside the scope of this guideline.

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				in liver disease) we suggest providing further detail regarding the risk factors for hepatitis together with the expected action regarding referral to specialist care as per NICE guidelines (PH43) and CDC guidance (please see http://www.cdc.gov/hepatitis/resources/professionals/pdfs/abctable.pdf). *Additional Risk factors for developing hepatitis include:* • *Age (60 years +)* • *Any risk factor for HCV or HBV:* o *Living in a high prevalence country: South Asia, Egypt, Italy, Eastern Europe, South America* o *Received any blood product or had a tattoo prior to 1991* o *Any medical procedure outside of the UK* o *Raised ALTs* o *History of or current Intravenous drug use* *Following initial investigation there should be prompt referral through to a hepatology specialist.*	
Gilead Sciences Ltd	Short	5 1.1.12	1	Clinical evidence suggests that there is a high degree of variability regarding the rate of progression of individuals with Hepatitis C regarding their level of cirrhosis. As such we believe that the offer of retesting for diagnosis of cirrhosis for those with Hepatitis C should be provided annually rather than every two years.	The GDG has now investigated the cost-effectiveness of decreasing the retesting interval from 2 years to 1 year, however this change was not cost-effective and so has not been recommended.
BASL	Short	4		The phrasing should be consider referral …	Thank you for your comment. Recommendation 1.1.10 does not include the word consider because this is a stronger recommendation. The GDG agreed that it was important that anyone diagnosed with cirrhosis should be referred to a specialist for initial assessment.
BASL	Full	135		In the UK UKELD is now in everyday use for identifying patients with a likely need for liver transplantation within and without liver transplant units and for decision making about listing within liver transplant units. In addition it is used frequently to make choices about which patients on the transplant waiting list should be prioritised. There is also an App in everyday use for these purposes. It is odd therefore that the emphasis here is on MELD rather than UKELD.	Thank you for your comment. UKELD was included within the literature search for risk assessment tools, however, no studies were identified assessing this tool meeting the inclusion criteria.
BASL	Full	140		The issue of screening for HCC in cirrhosis is contentious and there is no single view shared by all who expressed an opinion. A significant minority feel that the evidence does not support screening. But there is already pressure to screen based on international guidelines (AASLD & EASL). In contrast radiological societies in the UK and USA do not support the use of screening based on the same data. There is nothing in the guidelines that will alter the views of those who are already in an entrenched position. The conclusions need to reflect the view that screening is not equally effective in all patients with cirrhosis. It is increasingly effective in men, older patients and particular aetiologies including those with viral hepatitis, alcohol related liver disease and non-alcohol-related liver disease. A case could be made for reduced screening for women with autoimmune liver disease as single aetiology; not all agree. This might appear to be an area for further research but it is unlikely that future studies will look at liver US with AFP but instead at newer techniques as and when these arise. A clear steer is recommended to discuss cessation of screening in patients at risk of HCC in whom intervention could never be considered.	Thank you for your comment. The 'Recommendations and link to evidence' section discusses the clinical benefits and harms of surveillance and states that the decision to offer surveillance should be based on the ability to offer treatments for HCC. Recommendation 1.2.6 states that people receiving end of life care should not be considered for HCC screening.
BASL	Full	166		There is a recommendation that all patients with confirmed or likely cirrhosis should undergo endoscopic screening for varices. This is out of kilter with many centres who restrict screening based on other parameters such as platelet count.	Thank you for your comment. The GDG acknowledges that this recommendation may be a change of practice in some locations. Platelet count has a NPV of 79.9% in detecting OV and thus has not been shown to be an effective method to rule out oesophageal varices (Sebastiani, Tempesta et al. 2010). The GDG does not agree that this should be current UK practice. There is some evidence that a platelet count of >

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					150x109/L in combination with a liver stiffness measurement of < 20kPa may be able to exclude clinically significant portal hypertension, however data on the long term follow-up of this strategy does not exist (mortality and bleeding events) and the GDG felt this could not be the basis for a current recommendation. In current UK, European and North American Liver society guidelines endoscopic surveillance is recommended.
BASL	Full	172		Many centres now use carvedilol as prophylaxis, even though the evidence is based on propranolol. The conclusions should reflect that change in current practice.	Thank you for your comment. This guidance does not recommend the use of beta blockers for primary prophylaxis of variceal haemorrhage, and so does not take a position on which beta blocker(s) would be most appropriate.
Perspectum Diagnostics Ltd	General	General	General	The original scope laid out in Appendix A states that these guidelines will include the assessment of "non-invasive surrogate markers of cirrhosis", understand the usefulness of different tests for diagnosis and assessment of cirrhosis and cirrhosis severity. Specifically, Question 3 asks "*What is most accurate non-invasive imaging test to identify whether cirrhosis is present?*" (See also Chapter 6, p66, line 5). We were therefore surprised to see that final recommendations appear to have limited scope of the guidelines, and Question 3 limited to only a subset of the index tests available for monitoring and diagnosis and liver disease. Question 3 as scoped has therefore not been fully answered as these index tests, in turn, have been limited to only a subset of available non-invasive imaging tests in the UK NHS (see comment 2 below).	Thank you for your comment. All tests have been considered, and are included in the protocol. Please note that the protocol has now been edited to clarify all forms of MRI were included. However, for some tests no includable evidence was found (see comment ID20)
Perspectum Diagnostics Ltd	General	General	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, we would like bring two publications to the panel's attention, which appears to have been missed or been de-scoped from the clinical review. These publications are of high relevance to Questions 2-5: 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 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 14 patients with ISHAK fibrosis score ≥F4. Subgroup analysis has also been performed for different disease aetiologies, including n=36 patients with biopsy proven steatosis comparing 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. It is unclear whether this publication was identified in the clinical evidence search, but does not appear in the short list of clinical evidence considered in the final recommendations. We are concerned that this may represent an error of judgement, or potentially be an indication of selection bias to focus only on diagnostics that can be administered in a primary care setting. 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. 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 24 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 of cirrhosis and risk tools assessment, 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. The study uses	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) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there were insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. In addition, the study group did not specifically report a threshold for diagnosing cirrhosis (F5-6 in the Ishak scale). Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1). However we have taken the time to evaluate the paper and can inform you that it would have been 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 staging levels of fibrosis. Therefore the paper does not supply sufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool.

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				multiparametric MR imaging to characterise liver tissue, quantifying liver fat, liver iron (T2*), and fibro/inflammation (cT1), reported as a liver inflammation and fibrosis score (LIF) score. This LIF score was shown to have a 100% NPV in patients, irrespective of disease aetiology. While the publication includes analysis of mixed aetiologies, the lack of clinical evidence showing outcomes data for diagnostic tests makes inclusion of the this publication highly relevant. 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 (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 the review questions 2-5.	
Perspectum Diagnostics Ltd	Short	4	1-7	The limitations of the clinical evidence regarding the performance of transient elastography (TE) and/or acoustic radiation force impulse imaging (ARFI) in patients with NAFLD are well documented in the clinical literature, including the recent published European Association for Study of Liver (EASL) Clinical Practice Guidelines on non-invasive test for evaluation of liver disease severity and prognosis (J Hepatol, 2015, 63:237-264). While the GDG panel have correctly flagged the supporting evidence for this recommendation as low or very low quality, we are concerned that the recommendation in this guidance document will result in misdiagnosis of at-risk patients with advanced fatty liver disease and possible steatohepatitis. In addition to recommending a technique which is known to have a reduced success rate and diagnostic performance in very overweight/obese or patients, stratification relies on first obtaining a positive diagnosis using the enhanced liver test (ELF), according to the draft NAFLD guidelines. We have commented on the suitability of ELF test for stratification of NAFLD patients in the NAFLD guidelines response.	Thank you for your comment. Please see the responses of the NAFLD GDG to the comments submitted to the consultation on that guideline for discussion of the limitations of tests in people with NAFLD.
Perspectum Diagnostics Ltd	Full	13	22-27	See comment ID18 above.	Thank you for your comment. Please see the responses of the NAFLD GDG to the comments submitted to the consultation on that guideline for discussion of the limitations of tests in people with NAFLD.
Perspectum Diagnostics Ltd	Short	4	8-9	The recommendation to consider biopsy for diagnosis in people not suitable for TE may be challenging to implement. By limiting the scope of the clinical literature review to include only a subset of the available tests, this recommendation may have a negative impact on both patient journey and cost of diagnosis pathways for certain conditions.	Biopsy has previously been considered as an option for diagnosing cirrhosis, so this is not new. The preceding recommendations mean that a smaller group of people will now be considered for biopsy than has previously been the case. The clinical literature review included all available tests for which includable published evidence was available.
Perspectum Diagnostics Ltd	Full	13	28-29	See comment ID20 above.	Biopsy has previously been considered as an option for diagnosing cirrhosis, so this is not new. The preceding recommendations mean that a smaller group of people will now be considered for possible biopsy than has previously been the case. The clinical literature review included all available tests for which includable published evidence was available. Please note that all types of MRI are now included in the protocol for the relevant review, although no includable studies using MRI were identified.
Perspectum Diagnostics Ltd	Short	4	13-19	As highlighted in comment ID18, we are concerned about the emphasis that is being placed on the ELF test to stratify patients at greatest risk of disease progression. We have commented on the suitability of ELF test for stratification of NAFLD patients in the NAFLD guidelines response.	Thank you for your comment. Please see the responses of the NAFLD GDG to the comments submitted to the consultation on that guideline.
Perspectum Diagnostics Ltd	Full	13	33-38	See comment ID22 above.	Thank you for your comment. Please see the responses of the NAFLD GDG to the comments submitted to the

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					consultation on that guideline.
Perspectum Diagnostics Ltd	Full	65	10-11	This statement would be enhanced if the risk of complications was quantified, for example as a percentage.	Thank you for your comment. We feel that as this sentence is already referenced, a sufficient level of clarity is provided.
Perspectum Diagnostics Ltd	Full	65	26-28	This introduction lacks any discussion of imaging technologies available in UK that utilised magnetic resonance (MR) to evaluate cirrhosis by obtaining measures of liver "stiffness" (using magnetic resonance elastography, as described by Loomba et al., 2009, Clin. Gastroenterol. Hepatol.) or the liver inflammation and fibrosis (LIF) score (using multiparametric MRI, as described by Banerjee et al., J Hepatol, 2014). It is a limitation of both this introduction and the clinical evidence review that the scope of imaging assessment been limited to TE and ARFI and not the full range of available non-invasive imaging tools.	Thank you for your comment. The following sentence has been added to the third paragraph of this chapter introduction: "*Magnetic resonance elastography has also been used to assess liver fibrosis.*" Other MRI techniques are included in the literature review searches, with either no evidence found or papers excluded due to not fulfilling the criteria in the protocol.
Perspectum Diagnostics Ltd	Full	67	24-33	According to clinical evidence inclusion criteria specified Appendix C, Table 4, the multiparametric MRI publication highlighted in comment 2 by Banerjee et al., appears suitable for inclusion in so far as it: i) is a prospective, comparative, non-randomised study with comparison to reference standard of histological assessment; ii) has performed all liver biopsies using a length within the specified range of 15mm or more (median was 20mm, IQR 16-30mm); and >6 portal tracts (median was 10, IQR 8-15); and iii) performed the histological analysis using the ISHAK reference standard for fibrosis stage, with subgroup analysis for steatosis patients against Brunt NAS score. Given the limited number of publications identified and overall low quality of evidence evaluated, we consider this publication to be of high relevance for inclusion.	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) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there were insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. In addition, the study group did not specifically report a threshold for diagnosing cirrhosis (F5-6 in the Ishak scale).
Perspectum Diagnostics Ltd	Full	71	-	Table 18. It would be helpful to include the patient n number for each study in the summary table.	Thank you for your comment, we have added this information.
Perspectum Diagnostics Ltd	Full	78 – 96	-	Table 19 -28. Without exception, all studies identified in these tables used to assess the accuracy and usefulness of non-invasive imaging tests have been rated as 'low' or 'very low' in quality. It would therefore appear reasonable to assume that relevant evidence brought to the attention of the panel should be included in this assessment. We would urge the panel to consider inclusion of the above highlighted publications by Banerjee et al. and Pavlides et al in this regard.	The outcomes from these studies were rated low or very low using the GRADE methodology. However, these studies were first included in the review because they met the inclusion criteria outlined in the clinical review protocol. 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) the raw data associated with these sensitivity and specificity ratings were not provided and therefore there were insufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool. In addition, the study group did not specifically report a threshold for diagnosing cirrhosis (F5-6 in the Ishak scale).

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					Pavlides 2015 was published outside of our cut-off for inclusion (please see the Methods chapter section 4.2.1). However we have taken the time to evaluate the paper and can inform you that it would have been 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 staging levels of fibrosis. Therefore the paper does not supply sufficient data to populate the 2×2 tables required to analyse the diagnostic accuracy of the tool.
Perspectum Diagnostics Ltd	Full	102-105	1	We are concerned that a performance bias that has been attributed to TE and liver biopsy in the economic analysis performed and its impact on subsequent evidence statements. Firstly, line 4 states that TE has ranked first "*mainly due to having the highest diagnostic accuracy among the non-invasive tests*". We have already highlighted the clinical evidence discussing the relatively poor performance of TE in patients with NAFLD, particularly those who are overweight or obese. We are concerned that this recommendation may lead to the purchase of expensive equipment for a diagnostic test that will underperform in this patient population in clinical practice. Secondly, we are concerned by the statement that liver biopsy ranks first for cost-effectiveness in Hepatitis C patients (page 105, line 1). While the GDG panel and guidelines acknowledge that this is due in part to "*the fact that it was assumed it has a perfect sensitivity and specificity*", this raises concerns that trusts may limit access to therapy in the absence of biopsy-confirmed cirrhosis, which may result in patients at greatest risk of disease progression not obtaining treatment.	The review examined the clinical evidence for testing people with NAFLD for cirrhosis separately from testing other populations, and included using TE in people who were obese. In NAFLD there is the option of using either TE or ARFI, so there is no need to buy the relevant equipment to conduct one of these tests if the other is already available. Whilst noting in the evidence statement on page 106 that liver biopsy did indeed rank first in the original economic modelling at a cost-effectiveness threshold of £20,000 per QALY gained, the GDG has explicitly recommended that TE should be offered in preference to liver biopsy due to additional factors not taken into account in the modelling (including, but not limited to, the assumptions of perfect sensitivity and specificity). The discussion in the following 'Recommendations and link to evidence' table explains the reasons for that recommendation. There is hence no reason why an NHS trust would require a liver biopsy to diagnose cirrhosis except where TE is not possible.
Royal College of Nursing	General	General	General	The Royal College of Nursing welcomes the opportunity to review and comment on these draft guidelines. The RCN invited members who care for people with this condition to review and comment on its behalf. Some members of the British Liver Nurses' Forum also reviewed the draft guidelines and forwarded their comments to be considered as part of the RCN's submission. The RCN understands that the British Liver Nurses' Forum was originally on the stakeholder list but now seems to have been removed. The comments below reflect the views of the reviewers.	Thank you for your comment.
Royal College of Nursing	Full	General	General	The Cirrhosis draft guideline is commendable for the range of information that has been considered. By the development of these Cirrhosis guidelines it is hoped that the guidelines will set a benchmark for care to be delivered to ensure equity and consistency in the diagnosis, treatment and management of this condition.	Thank you for your comment.
Royal College of Nursing	Full	44	6	Primary biliary cirrhosis has now been renamed Primary Biliary Cholangitis	Thank you for your comment. We acknowledge that this terminology has changed since the time of writing, and has been changed in the guideline accordingly. The term has also been added to the glossary.
Royal College of Nursing	Full	60	20	NICE PH43 identifies the risk groups that should be tested for Hepatitis B and C. It would be useful to make reference to this document to offer clarity and breadth of people that should be considered for testing.	Thank you for your comment. This guideline does not look at the identification of hepatitis B or C. This

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					guideline only covers from the point of a positive diagnosis of hepatitis B or C.
Royal College of Nursing	Full	63		Primary biliary cirrhosis has now been renamed Primary Biliary Cholangitis	Thank you for your comment. We acknowledge that this terminology has changed since the time of writing, and has been changed in the guideline accordingly. The term has also been added to the glossary.
Royal College of Nursing	Full	65	11	Spelling error should read practitioner	Thank you for your comment. This has been amended in the full guideline and appendices documents.
Royal College of Nursing	Full	66	Table 16	Primary biliary cirrhosis has now been renamed Primary Biliary Cholangitis	Thank you for your comment. We acknowledge that this terminology has changed since the time of writing, and has now been changed in the guideline accordingly. The term has also been added to the glossary.
Royal College of Nursing	Full	68	12	Primary biliary cirrhosis has now been renamed Primary Biliary Cholangitis	Thank you for your comment. We acknowledge that this terminology has changed since the time of writing, and has been changed in the guideline accordingly. The term has also been added to the glossary.
Royal College of Nursing	Full	106	44	Primary biliary cirrhosis has now been renamed Primary Biliary Cholangitis	Thank you for your comment. We acknowledge that this terminology has changed since the time of writing, and has been changed in the guideline accordingly. The terminology has also been added to the glossary.
Royal College of Nursing	Full	106	45	Primary biliary cirrhosis has now been renamed Primary Biliary Cholangitis (PBC)	Thank you for your comment. We acknowledge that this terminology has changed since the time of writing, and has been changed in the guideline accordingly. The terminology has also been added to the glossary.
Royal College of Nursing	Full	113		We note that PBC is correctly named here?	Thank you for your comment. All instances have now been changed.
Royal College of Nursing	Full	139		Recommend a Model For End-Stage Liver Disease (MELD) calculator for consistent use across the country as some practitioners may not be familiar with MELD calculators. Suggest add a link to the MELD calculator.	Thank you for your comment. MELD calculators are freely and easily available online, and are commonly used by hepatologists.
Royal College of Nursing	Full	139		The lack of evidence around United Kingdom Model for End Stage Liver Disease (UKELD) means that it has not been considered. UKELD is used routinely in all superregional and tertiary centre so there may be an opportunity to make a research recommendation here to investigate the robustness of UKELD.	Thank you for your comment. Extra clarifications were added to the relevant LETR. UKELD is a specific UK score designed by the Liver Advisory Group of NHS Blood and Transplant to evaluate the risk/benefit of referral for Liver Transplantation. It is used exclusively for this purpose in the UK, and there is an evidence base to support this. UKELD is not used, or validated for routine use in the prediction liver related mortality or morbidity outside of the setting of referral for liver transplantation, a role where MELD is well established. Therefore, UKELD was not recommended as an evidence-based score to prompt referral to specialist hepatology care. The GDG did not recommend further research into this risk prediction tools because we acknowledge that there is currently an ongoing project, led by NHS Blood & Transplant, to replace UKELD and modify the system of organ allocation in the UK.
Royal College of Nursing	Full	235		Section 15 hepatic encephalopathy – acute episode is addressed but not on-going management. Having reviewed the other sections it does seem as those on going management is addressed for other complications.	Thank you for your comment. During development the GDG were unable to include the area of chronic hepatic encephalopathy, due to the on-going NICE TA337. It

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					was then identified that management of acute hepatic encephalopathy would not be included in the TA and so this area was included for review.
Royal College of Nursing	Full	General	General	Throughout the document there appears to be the use of American terminology rather than UK terminology such as hematemesis rather than haematemesis; thrombocytopenia rather than thrombocytopaenia. It would be helpful to use UK terminology to avoid confusion.	Thank you for your comment. We have amended the full guideline and appendices documents to reflect the UK spelling 'haematemesis'. We have not amended the spelling of 'thrombocytopenia' as this is the accepted UK spelling and is consistent with NICE style.
Royal College of Radiologists	Full	140 - 162	General	There have been two systematic reviews published into the value of ultrasound (US) surveillance with conflicting conclusions (Kansagara et al, Annals of Internal Medicine, 2014; Singal et al, PLoS Medicine 2014) respectively pooling 22 and 36 studies. In the absence of randomized, controlled trials these are based on non-randomised studies (NRS) that have been published. Only six were eligible for inclusion for the comparison of surveillance vs. no surveillance. No data was available for many the pre-specified critical outcomes. The evidence supporting the recommendation for US surveillance is acknowledged by the GDG as poor at best.	Thank for your comment. The references in the 2 systematic reviews you refer to were cross-checked for any relevant studies and included to our review. The quality of the evidence in our review is discussed in the 'Recommendations and link to evidence' section.
Royal College of Radiologists	Full	140 - 162	General	The types of study included in the guideline have inherent weaknesses such as the presence of lead time and length bias. Whilst these are to some extent acknowledged by the guideline development group (GDG) it is difficult to adequately control for these. As the studies only include patients with HCC detected with or without a surveillance program the magnitude and effect of false positives cannot be measured. As in practice most nodules detected with US whether true or false positive are initially indeterminate, there will be an unquantified number of ongoing investigations that would be generated before a diagnosis is established, the next investigation usually being MRI in the UK (although the guidelines from most liver societies also allow multiphasic CT). A proportion, especially small lesions, will remain indeterminate after the first additional test and require further follow up. In the paper by Trinchet 2011[(233)] comparing a 3 and 6 monthly regimen, 65% of the nodules detected by US were false positives.	Thank you for your comment. Studies were downgraded for quality, if relevant, for lead time and length bias. These sources of bias are discussed in both the introduction and the 'Recommendations and link to evidence' section. The following sentence has been added to the 'Recommendations and link to evidence' section: "*As the studies only include patients with HCC detected with or without a surveillance program the magnitude and effect of false positives cannot be measured.*"
Royal College of Radiologists	Full	140 - 162	General	The underlying aetiologies of cirrhosis in the populations included in the analysis are dominated by viral hepatitis although the aim is to reduce studies containing patients with hepatitis B. The relative exclusion of hepatitis B surveillance is on the grounds that it is recommended in CG165 for patients with chronic hepatitis B infection. It is worth noting, however that the evidence supporting surveillance for the early detection of HCC in individuals with chronic hepatitis B infection, was not assessed in CG165. The review question was phrased to determine how frequently, rather than if surveillance for HCC detection should be done.	Thank you for your comments. Recommendations for an HBV population were made in the HBV guideline. The scope of the Cirrhosis GL was not to update this topic. However, we do acknowledge that although this was covered in the HBV guideline they did not look at the evidence for surveillance vs. no surveillance (ie. whether surveillance was effective), but rather they looked at the evidence for frequency. The GDG in the HBV guideline must have considered that surveillance was necessary and therefore did not look at the evidence for its effectiveness per se, but thought that the important question to address was how often it should be done.
Royal College of Radiologists	Full	140 - 162	General	The diagnostic performance of US cannot be expected to be uniform in all causes of cirrhosis and it is not clear that this heterogeneity is reflected in the analysis. The habitus of a population of patients with non-alcoholic fatty liver disease (NAFLD) would be expected to differ from patients with viral hepatitis for example, with many of the NAFLD group being obese. The performance of trans-abdominal US is generally poorer in the obese and NAFLD is under represented in the study groups when compared with the UK population. The annual incidence rate varies (and therefore prevalence of HCC) in the screened population depending upon the cause of the cirrhosis, being highest in patients with viral hepatitis. A further potential cause of heterogeneity in performance is the variable rate of false positives dependent upon the cause of the cirrhosis e.g. for Trinchet 2011[(233)] the rate of false positives was highest for patients with alcohol related liver disease.	Thank you for your comment. The data for this question were from observational studies and were not meta-analysed. Heterogeneity cannot therefore be assessed through statistical analysis. However, the difference in results is discussed narratively in the 'Recommendations and link to evidence' section. We have now added 'obesity' to the examples of where accuracy of ultrasound may be in reduced in the 'Recommendations and link to evidence' section on page 162.
Royal College of Radiologists	Full	140 - 162	General	Due to the nature of the studies included in the guidance the impact of comorbidities on the mortality and morbidity cannot be adequately addressed. For example the NAFLD population with a high incidence of cardiovascular	Thank you for your comment.

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				morbidity and morbidity may have less to gain from US surveillance than a population with viral hepatitis and a lower prevalence of such conditions.	The GDG was not able to identify data giving the risk of cardiovascular mortality specifically in people with NAFLD. However, we note that surveillance for HCC in the NAFLD population was found to be more cost-effective in people with NAFLD than in people with hepatitis B, which is already recommended, and this would remain the case even if the non-liver-related mortality in people with NAFLD was increased by a significant proportion.
Royal College of Radiologists	Full	140 - 162	General	The comment from the patient perspective that patients would want to be monitored is important. Due to the nature of the studies that are described, there is no quantification of the benefits to the individual with cirrhosis considering surveillance. A relative risk reduction in mortality from HCC once HCC has developed is relevant but the individualised risk of developing HCC is also important. Many patients undergoing surveillance will not develop HCC but a proportion (that is not quantified in this review) will be harmed as a consequence of participation. The harm would increase if the guidance of specialist societies were to be followed more closely than is current UK practice, where there is a recommendation for indeterminate nodules that are 1-2cm in diameter to be biopsied after the second diagnostic test. There is also a shift to ablate some of these lesions prior to a tissue diagnosis and therefore some of these will inevitably be benign. The comment that it would be a disservice to patients not to offer surveillance for the early detection of HCC is an illustration that the harms of surveillance may be underestimated. It is perhaps not surprising in that context that patients would opt to have surveillance.	Thank you for your comment. The GDG agrees that it is difficult to quantify the benefits and harms to any individual of surveillance, however we have added a sentence to the 'Recommendations and link to evidence' section to make it clear that the risks and benefits should be discussed with the patient. Guidance on shared decision making can be found in NICE CG138: Patient experience in adult NHS services, specifically, recommendation 1.5.22.
Royal College of Radiologists	Full	140 - 162	General	There is an assertion in the summary of the guidance that HCC surveillance is done routinely in clinical practice. The *ad hoc* provision of surveillance for HCC in the UK has recently been assessed (Cross et al, Frontline Gastroenterology, 2016) and although this would not have been available to the GDG, it is clear from that report that full compliance is not taking place for the majority of patients. Surveillance as currently practiced is likely to reduce its effectiveness. The full implementation of this guidance would have resource implications with many trusts struggling to deliver the increase in number of US and follow on MR examinations that the programme would generate. It is difficult to mitigate against such an increase in workload without increased resource, as Radiology departments are already finding it difficult to meet current demand in a timely manner.	Thank you for your comment. The GDG notes that Cross 2016 states that HCC surveillance is currently undertaken in almost all liver units reporting current practice (97%) and that this is every 6 months in a majority (62%). The GDG agrees that HCC surveillance is however not currently conducted universally, or systematically for each patient. The GDG agrees that making HCC surveillance more systematic and consistent would improve its effectiveness, and hence has recommended this. The resource implications of implementing this guidance are assessed in the NICE resource impact tool for this guideline.
Royal College of Radiologists	Full	140 - 162	General	The outcome of the cost effectiveness analysis on the basis of aetiology of cirrhosis is perhaps surprising, although the parameters upon which the model was based are not entirely clear. It is noted that part of the justification for accepting the recommendation of US surveillance above £20,000 per QALY is on the basis of the costs of non-HCC complications. Given that these factors were not assessed it is difficult to predict how they would affect the modelling.	All parameters and assumptions on which the model was based are detailed in Appendix N. We agree that it is not possible to quantify any additional benefit from identifying non-HCC complications. However the GDG felt that patients could further benefit from HCC surveillance when this is part of an integrated package of surveillance for other complications of cirrhosis since ultrasound can also assess portal hypertension, portal vein thrombus and ascites.
Royal College of Radiologists	Full	140 - 162	General	On the basis of the evidence provided it is difficult to determine whether or not US surveillance provides a survival benefit for all patients with cirrhosis, or a survival benefit for patients with cirrhosis from a specific group of aetiologies. The cost effectiveness as presented appears to be on the margin of the usually accepted economic threshold. Current practice, as described by Cross et al, Frontline Gastroenterology, 2016 appears to be the worst of all worlds and it would seem unlikely that the guidance would be sufficient to persuade the UK National Screening Committee to take on the running of a dedicated managed service. The GDG seem doubtful that a	Thank you for your comment. The National Screening Committee is responsible for advising on and implementing population screening programmes, not surveillance programmes in people with an existing condition, and therefore they would not

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				randomised controlled trial could be performed and this guidance will make it less likely that high quality evidence could be obtained in the UK.	be the body responsible for organising or auditing HCC surveillance nationally. The GDG does not believe it likely that an RCT could ever be carried out in the UK, and so a decision for or against HCC surveillance needs to be taken now based on the (mixed) existing evidence. The GDG therefore does not think that the implementation of this guidance will make a future RCT less likely, however it would provide a direct opportunity for new observational studies to be conducted.
Royal College of GPs	Full	General	General	This a comprehensive and well written document, largely for clinicians and support teams in secondary care. It would be helpful to have some more information of the natural history of the disease and whether it differs with the aetiology i.e. alcoholic cirrhosis worsened by continued drinking, reversible or arrested if alcohol completely avoided. Cirrhosis is the final common pathway from various liver insults from lifestyle, environment and genetic predilection The particular difficulty is with Hepatitis C and the proportion of people so infected who will go on to develop cirrhosis and over what sort of time period i.e 5-25 years or never. Is the patient with Hepatitis C more at risk of cirrhosis if they drink alcohol even at acceptable levels. The possibility of a vaccine against Hepatitis C is crucial and /or its early treatment and cure. The evidence that HepB vaccination protects against liver cancer and cirrhosis seems established. (PS)	Thank you for your comment. This level of detail is outside the breadth of this guideline. Please note that NICE has produced separate guidelines on alcohol misuse, hepatitis B and NAFLD.
Royal College of GPs	Full	General	General	Much of the guideline seems to be driven by a desire for earlier diagnosis or better prediction of complications. While one can understand the desire of specialists to be able to predict the future, in practice the value of earlier diagnosis or prediction of complications would depend on robust evidence that early intervention would be more effective. It is not clear there is evidence of that, for instance knowing that a male patient is drinking more than 50 units a week would be enough to try to persuade him to stop drinking altogether, whether or not there is any evidence of liver damage. The critical question is whether a professional advice would carry more weight if backed up by evidence of existing cirrhosis. Again does such evidence exist, because without it a lot of this otherwise admirable work looks irrelevant. I would be interesting to see the particular evidence concerning NAFLD but it's clear that this exists in a separate guideline. (DJ)	Evidence for the clinical and cost-effectiveness of earlier diagnosis is demonstrated in the results of the cost-effectiveness modelling conducted for this guideline, which can be found in Appendix N and is summarised and discussed in Chapters 5–9. We note that you have also commented on the consultation on the NAFLD guideline, and those comments have been replied to by the NAFLD guideline team.
Royal College of GPs	Full	12		The effect of the algorithm could be that all patients where the GP is worried about their alcohol intake would be referred for tests for cirrhosis (whose various competing merits are discussed later in the guideline). But this potentially could create a huge demand for expensive tests. Has the GDG considered the practical, medical and financial implications of this recommendation? (DJ)	Thank you for your comment. In line with the recommendations in this guideline, it was intended that people misusing alcohol should only be tested if they have either been diagnosed with alcohol-related liver disease or drink at hazardous levels. In order to minimise any confusion the risk factors at the start of the algorithm have now been separated from the rest of the flow diagram.
Royal College of GPs	Full	30	14/15	'Sensitivity considered more important than specificity' The group considers missing a diagnosis more important because of the consequences of missing a diagnosis. Has the group failed to consider the consequences of the false positive results? Particularly in the apparent absence of evidence that earlier diagnosis will make a difference (see above). (DJ)	The consequences of false positive results were fully included within the cost-effectiveness modelling conducted for this guideline (along with false negative, true positive and true negative results).

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Royal College of GPs	Full	44	4.	*The GDG thought that it would be helpful to identify people at risk of having cirrhosis before they developed evidence of liver decompensation.* See comment above under 'general'. It might be helpful, but the guideline does not give us any evidence to support the contention. One hazard is that, once a tool and target groups have been identified some enthusiastic person will want to have it included in QOF scores. One specific omission was a consideration of the value of GGT tests on those with high alcohol intake to distinguish those where liver damage is already happening. (DJ)	This sentence has been reworded to replace 'would' with 'might' to reflect the fact that this statement is in the introduction which precedes the evidence review, and thus reflects the GDG's opinion before conducting the review. The subsequent review, together with the results of other evidence reviews in this guideline and the economic modelling in Appendix N, subsequently demonstrated that identifying people with cirrhosis at an earlier stage did have benefits in terms of reduced variceal bleeding, earlier detection of cancer, increased life years and increased QALYs, and was cost-effective compared to not testing for cirrhosis. GGT is a non-specific test which is neither sensitive for alcohol related liver injury or liver fibrosis/cirrhosis. The GGT is increased in liver disease due to non-alcohol-related fatty liver, drug-induced liver injury and cholestatic liver injury (PBC, PSC sarcoisosis etc). There is no evidence base to support its use in the context of identifying those with alcohol-related liver disease from other causes of liver injury.
Royal College of GPs	Full	61		Statements are made here that are inconsistent. In the same paragraph is stated that the GDG found it difficult to define a cutoff level, and then both proceed to do so (>50 units per week for men; >35 units per week for women), and then say that there could be a case for testing some who drink less than these levels under some (unstated) circumstances. (DJ)	. Thank you for your comment. The GDG acknowledged that it is difficult to define a cut-off level, however it is necessary to do so to create guidelines that can be implemented in practice, and so the GDG selected the NHS definition of 'higher-risk' drinking as published in NICE guidance PH24 Alcohol use disorders: preventing harmful drinking as the most appropriate cut-off level, this being the accepted level in the UK for harmful drinking. However, the GDG also accepted that there may be exceptional cases where doctors believe it necessary to test people who were not drinking at harmful levels (for example drinking at a hazardous level for a very long time), and so the GDG also made clear that testing people drinking below these limits should not be prohibited in all circumstances.
Royal College of GPs	Full	67	18	According to classical teaching on tests, the sensitivity and specificity are not affected by prevalence; it is the positive and negative predictive values. In reality, if these tests were more widely used in primary care then the population being tested would in time come to include large numbers of healthy individuals, and this does not seem to have been taken into account. (DJ)	Thank you for your comment. This guideline does not advocate the testing of healthy individuals, and is only targeted to people with identified liver diseases.
Royal College of GPs	Full	67	41-48	This paragraph contains the limitations of reference standard tests, which is crucial in this guideline. (DJ)	Thank you for your comment
Royal College of GPs	Full	112		The group comments on inconsistent results in the NAFLD group of patients. I wondered whether this might be explained at least in part by inconsistency in the diagnostic criteria (or their application) for the appearance of NAFLD itself. (DJ)	Thank you for your comment. This inconsistency could potentially be attributed to the differing aims of every study.
Royal College of	Full	138	Top of	*GDG members discussed that currently, in their opinion, there are a large number of patients with compensated*	Thank you for your comment. This has been noted.

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GPs			page	*cirrhosis who are not referred to specialist hepatology services until they have an episode of decompensation.* Doctors – either primary care or specialists in other disciplines – are not referring to specialist hepatologists patients whom they know or have strong suspicions of cirrhosis. (DJ)	
Intercept Pharmaceuticals	Short	3	3	We suggest adding 'primary biliary cirrhosis/cholangitis (PBC)' to the list. PBC is recognised in the full guideline as a cause of cirrhosis and therefore for consistency we believe it should be included in the short guideline. Data from Corpechot [(1)] supports the rationale for doing so. Corpechot demonstrated that the incidence of cirrhosis after 5 years of UDCA treatment was 4%, 12%, and 59% among patients followed-up from stages I, II, and III, respectively. At 10 years, the incidence was 17%, 27%, and 76%, respectively. The median time for developing cirrhosis from stages I, II, and III was 25 years, 20 years, and 4 years, respectively. 1 Corpechot C et al. Primary biliary cirrhosis: incidence and predictive factors of cirrhosis development in ursodiol-treated patients. Gastroenterology 2002; 122(3):652-8	Thank you for your comment. The GDG acknowledges that this may be one of many risk factors for cirrhosis. This is noted in the chapter introduction on page 45. However, the evidence review protocol included only those deemed by the GDG to be the most major risk factors for cirrhosis.
Intercept Pharmaceuticals	Short	4	24	We suggest adding "all people diagnosed with primary biliary cirrhosis who have a previously defined abnormal bilirubin". Mayo [(2)] illustrated that event free survival was significantly lower in people with high baseline enhanced liver fibrosis (ELF). Each 1 point increase in ELF was associated with a 3 fold increase in future complications. 2 Mayo M et al. Prediction of Clinical Outcomes in Primary Biliary Cirrhosis by Serum Enhanced Liver Fibrosis (ELF) Assay. Hepatology 2008; 48(5): 1549-1557	Thank you for your comment. The less prevalent causes of cirrhosis are not specified within this recommendation.
Royal College of Pathologists	both	general	general	I found these guidelines clear, very well evidenced, and a really useful piece of work. I have some specific comments relating to the pathology of cirrhosis and use of biopsy in diagnosis.	Thank you for your comment.
Royal College of Pathologists	Short	6	23-25	"It is characterised at a cellular level by distortion of the normal liver structure into nodules of liver tissue surrounded by fibrosis". - I suggest change to 'alteration of the liver structure from the normal soft, smooth texture into a more rigid organ of nodules of liver tissue surrounded by fibrous scar tissue' so that the abnormality of 'cirrhosis' is due to scarring and can be related to the increased liver stiffness.	Thank you for your comment. We believe that the current wording is clearer.
Royal College of Pathologists	Full	13	28-29	"Liver biopsy in whom transient elastography is not suitable" - from p112, this is specifically related to ALD patients currently drinking, increased stiffness is due to swelling and protein retention in liver cells. If this is what is referred to, it would be useful to include that text on p13. Consider including mention of other situations where high estimate of liver stiffness, e.g. acute hepatitis, congestion in venous outflow obstruction,	Thank you for your comment. NICE recommendations are intended to give a short but clear summary of actions that should be taken. More information, including examples of some scenarios in which transient elastography may not be suitable are given in the 'Recommendations and link to evidence' table, but these are not intended to be comprehensive or override clinical judgement, and therefore the GDG did not think it appropriate to include them in the recommendation. As you state, the GDG notes that ALD patients who are currently drinking have unreliable TE results due to increased liver stiffness (page 114 and 118). However, the GDG also notes that for people with hepatitis C who prefer biopsy over TE (page 117), and potentially in some cases people with NAFLD (pages 117-118) may also be considered for liver biopsy.
Royal College of Pathologists	Full	67	22 and 28	'There are known to be limitations with using liver biopsy for the diagnosis of cirrhosis. For example, the accuracy of liver biopsy can be affected by sampling errors and fibrosis heterogeneity within the liver itself. These inaccuracies are accentuated in biopsy samples of inadequate size. The UK standard criteria for an adequate biopsy length is ≥25 mm and containing at least 10 portal tracts.' 'The GDG also set a lower limit for the size of the biopsy, at which any studies including all or a proportion of biopsies below this lower limit would be excluded. This lower limit was set at 15 mm and 6 portal tracts, as the GDG felt that below this level the accuracy of the biopsy would be severely compromised and an accurate level of fibrosis would not be possible to assess.' This is in line with the Royal College of Pathologists Tissue Pathways for the investigation of medical liver disease, March 2014. The GDG may consider referencing this, in quoting 'the UK standard criteria'.	Thank you for your comment and reference.

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				The longer 25mm standard is necessary for reliably assessing the fibrotic architecture of the liver ('fibrosis stage'), the width of the biopsy is also important, with 16G needle needed to deliver a specimen near to1mm diameter. Cirrhotic nodules are usually >1mm, and in macronodular cirrhosis >3mm - so cannot be reliably recognised in a short narrow specimen. The lower limit of 15mm 6 portal tracts is usually sufficient for diagnosing the type of disease (fatty liver, chronic hepatitis etc.) but will underestimate fibrosis stage in some patients, depending on sampling error in the liver more than inter-observer variation. I agree that exclusion of studies with a smaller biopsy size is appropriate. If liver biopsy is being used to confirm cirrhosis in an individual patient, the same comments on the importance of an adequate biopsy sample apply, and clinicians must know that the quality of the biopsy is particularly important when it is being done for specifically for staging rather than diagnosis of the cause of the liver disease. Many biopsies currently taken in the UK are very much smaller than the 15mm minimum described here, and therefore carry the risks of liver biopsy without the contribution to accurate diagnosis.	
Royal College of Pathologists	Full	111	3-5	'The GDG specified in the protocol the most commonly used biopsy scoring systems for cirrhosis, including Knodall F4, Ishak F5/6, Metavir F4 or, for NAFLD populations, the Kleiner or Brunt scoring systems.' I think the guidelines should also specify that Kleiner or Brunt system is F4, cirrhosis. Earlier in this guideline (p62) and also in the NAFLD guideline, there is reference to bridging fibrosis, (Kleiner/Brunt stage 3) as the threshold for patient diagnosis and intervention, which may result in ambiguity unless F4 is explicit in this sentence. (Knodell - is spelt with an 'e')	Thank you for raising this. 'F4' has been added to this sentence as you suggest. The spelling error has now also been corrected.
Royal College of Pathologists	Full	115	4th paragraph	Regarding liver biopsy in hepatitis C: 'It is also considered highly unpleasant by patients, leading to a very low acceptability among patients.' I am concerned that to say liver biopsies are "considered highly unpleasant by patients, leading to a very low acceptability among patients" in this document which is read by patients, may deter them from having a biopsy which may be clinically important to them (both hepatitis C and other causes of cirrhosis) and become a self-fulfilling prophecy. I have discussed with my hepatology colleagues - there is a place for liver biopsy in the diagnosis of cirrhosis, based on the clinical decision of patient and clinician, "I find that liver biopsies are generally well tolerated. Patients don't like them, but if the benefits are explained in terms of accurate diagnosis, then patients will go with them." For patients suspected of having cirrhosis based on fibroscan/Elf in a young patient, with the effects on future life, insurance, surveillance investigations, etc. the risk of over-estimating fibrosis by non-invasive tests should be explained and the option of biopsy to confirm the diagnosis should be offered. A quick look at our patients with fatty liver disease and fibroscan >16kPa who opted to have have a liver biopsy - less than half those having a biopsy had bridging fibrosis or cirrhosis. If a biopsy is done, the specimen size is important, as discussed above.	Thank you for your comment. The word 'highly' has now been removed from this sentence. The GDG agree that there may be a place for liver biopsy in some cases, as reflected in the recommendations. This point was however raised both by clinicians and patient representatives, and is important to include as part of an honest weighing up of the benefits and downsides of each test. The GDG's recommendations sum up the decisions made on the basis of all the benefits and harms.
Norgine Pharmaceuticals Ltd	FULL	General	General	Norgine would like to thank NICE and the guidelines committee (GDG) for highlighting the need for a full appraisal of Cirrhosis. The guideline should enable clinicians, nurses and commissioners to identify, diagnose, and manage patients with cirrhosis and its related complications with clear direction within both secondary and primary care. Whilst we welcome this guideline, Norgine would like to highlight that the cirrhosis guideline is currently incomplete, since it does not review, or make recommendation on all of the major complications of cirrhosis, including long term management of Hepatic Encephalopathy (HE) and portal hypertension, other than in the context of varices, which were not explicitly excluded at the scoping stage of the process (see scoping document for reference).	Thank you for your comment. NICE guidelines focus on areas of uncertainty or variability in practice. The issues identified in the scope have been fully considered.
Norgine Pharmaceuticals Ltd	Full	1	1	The title of the guideline infers that it is a comprehensive review of the assessment and management of cirrhosis, so that, this should be the definitive source of information where clinicians, nurses and commissioners will refer to, in order to fully manage their patients and/or commission the re-design of locally implemented liver services. As the	Thank you for your comment. NICE guidelines focus on areas of uncertainty or variability in practice. The issues

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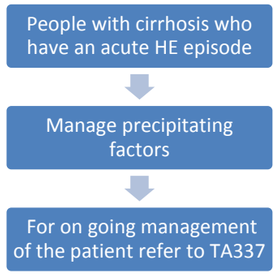
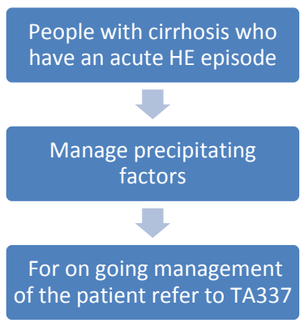
				guideline does not include all of the major complications, nor does it make any cross reference to other guidelines (e.g. referral for liver transplantation) we suggest that additional sections are required in this guideline to cover all major complications, otherwise the title should be amended to reflect the incomplete or partial nature of the guideline.	identified in the scope have been fully considered.
Norgine	Full	12	2	Within the complications section of the algorithm, ascites, upper GI complications including variceal bleeding and TIPS are all covered but the management of patients with an acute episode of HE, or their ongoing management to reduce the incidence of further acute episodes, is missing. The content of section 15, on acute HE, is completely missing from the algorithm and Norgine request that it is included since it has been identified by the GDG as an important complication of cirrhosis. Without its inclusion, Norgine feels that the algorithm is incomplete by not providing the intended audience with all the information to manage their patients. There is little or no reference to the importance of on-going management of HE patients beyond the acute phase. Norgine believes this has the potential to put patients at risk, as the absence of any guidance for clinicians may lead to some patients having their acute treatment maintained inappropriately and other high-risk patients receiving no treatment. The final version of the algorithm should reflect the entire content of the clinical guideline, since the algorithm is likely to act as the key reference point for clinicians, nurses and commissioners. Norgine therefore suggest, the following flow to be added to the complications section of the algorithm: 	Thank you for your comment. The algorithm is intended to show a visual representation of the recommendations in this guideline. The management of acute hepatic encephalopathy does not feature in the algorithm because no recommendations were made. NICE Pathways will link the recommendations in this guideline to other NICE recommendations on liver disease, including recommendations from NICE technology appraisals. The reference to TA337 has now been moved from Section 15.6 to Section 15.1, page 237, at the end of the chapter introduction, where it is more appropriate.
Norgine	Full	12	2	There are inconsistencies within the algorithm, as some sections make reference to NICE TAs or NICE CGs (e.g. reference to surveillance test for Hep B CG165 is included), and other sections do not refer to any NICE TAs or NICE CGs, even though they are available. Within the complications section, we believe that the algorithm should refer to TA337 in order to direct clinicians to the appropriate long term management of chronic and covert HE patients. Norgine therefore suggest the inclusion of the following flow: 	. Thank you for your comment. The algorithm is intended to show a visual representation of the recommendations in this guideline. The cross-referrals to other NICE guidance appear in the algorithm because they are contained within recommendations made in this guideline, as these cross-referrals directly answer review questions asked in this guideline for some or all of the populations under study. A cross-referral to TA337 is not part of any of the recommendations in this guideline. Please note that the NICE pathway will include all related NICE guidance.

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Norgine	Full	12	2	Within the surveillance section of this guideline, there is no mention of covert HE as a major complication in patients with cirrhosis, and yet, covert HE is very common, affecting up to 80% of patients with cirrhosis (Cichoz-lach H, et al. World J Gastroenterol 2013; 19(1): 26-34). Covert HE has been associated with, increased risk of developing overt HE, increased risk of hospitalisation and increased mortality (Jepson P, et al. Hepatology 2010;51:1675-1682, Bustamante J, et al. J Hepatology 1999;30:890-895). Patients with cirrhosis who have an observed and meaningful decline in QoL, work productivity, short-term memory and reduced attention span, may benefit from screening to allow proactive management of precipitating factors and symptoms. Therefore it is important that screening for covert HE should be included as part of the "surveillance" section of the algorithm and the diagnosis section. Screening for covert HE should recommend inexpensive and validated testing strategies, for example neurocognitive tests (PHES and Stroop).This has not yet been covered by any CG or TA to our knowledge.	Thank you for your comment. Surveillance for covert hepatic encephalopathy was not an area identified by the GDG as a priority for this guideline.
Norgine	Full	12	2	Within the surveillance section of this guideline, Norgine believes the addition of the text box would strengthen the recommendation within the "complications" section in the algorithm. Addition of a new text box which states *"consider a referral for liver transplant if HE or SBP is present, as patients with MELD scores above 12/15 with episodes of variceal bleed, ascites or SBP, should be considered for referral."* This will ensure that the guidelines remain consistent with the current transplant guidelines (O'Grady D et al. BSG Guidelines in Gastroenterology. 2000, Liver Transplantation: Selection Criteria and Recipient Registration 2015: POLICY POL195/4).	Thank you for your comment. The algorithm is intended to show a visual representation of the recommendations in this guideline. This guideline recommends referral of people with, or with a high risk of, complications to a specialist hepatology centre.
Norgine	Full	13	14	For consistency, Norgine suggests that NICE guidance as well as NICE guidelines should be included in the current text. We suggest the text is amended to: *"Also see the NICE guidelines and NICE guidance on: non-alcoholic fatty liver disease (NAFLD), alcohol use disorders: diagnosis and clinical management of alcohol-related physical complications NICE CG 100, alcohol use disorders: preventing harmful drinking NICE CG115, alcohol use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence NICE PH 24, type 2 diabetes, obesity and hepatitis B (chronic) NICE CG165 and for ongoing management of HE NICE TA337."*	Thank you for your comment. This recommendation is regarding risk factors for cirrhosis, to which the guidelines listed are directly relevant. Cross-referring to the NICE TA337 would not be appropriate here as it is not a risk factor for cirrhosis. Please note that the NICE pathway will include all related guidance.
Norgine	FULL	14	42	Norgine suggests that a new text box should be included within the complications section of the algorithm to cover the management of acute HE. *(Please see diagrams within comments 3 & 4 above)*	Thank you for your comment. The algorithm is intended to show a visual representation of the recommendations in this guideline. No recommendation was made regarding the management of acute hepatic encephalopathy.
Norgine	FULL	14	43	Norgine suggests the addition of new boxed wording within the complications section of the algorithm from line 42 *"Manage the precipitating factors" (Please see diagrams within comments 3 & 4 above)*	Thank you for your comment. The algorithm is intended to show a visual representation of the recommendations in this guideline. No recommendation was made regarding the management of acute hepatic encephalopathy.
Norgine	FULL	14	44	Norgine suggests the addition of new boxed wording within the complications section of the algorithm from line 43 *"For on-going management of the patient refer to TA337" (Please see diagrams within comments 3 & 4 above)*	Thank you for your comment. The algorithm is intended to show a visual representation of the recommendations in this guideline. No recommendation was made regarding the management of acute hepatic encephalopathy.
Norgine	FULL	15	20	Norgine recommends a new research question to be considered to assess whether certain interventions could affect the rate/ outcome of liver transplantation. The new research question proposed is*" What is the impact of ongoing pharmacological interventions for HE on subsequent liver transplantation"*.	Thank you for your comment. Research recommendations are based on key uncertainties identified through the evidence reviews that are likely to inform decision-making and, as such, the GDG did not identify this as a topic for a research recommendation.
Norgine	FULL	15	20	Norgine recommends a new research question related to the epidemiology of HE. Norgine is aware that currently there is no ICD code for HE, and that patients with HE are currently coded using a variety of different ICD codes and thus there is little or no data on the actual burden of patients with HE on the NHS. The new research question proposed is*" What codes are currently used for patients with HE, can we reliably calculate the incidence and*	Thank you for your comment. Research recommendations are based on key uncertainties identified through the evidence reviews that are likely to inform decision-making and, as such, the GDG did not

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				prevalence of HE based on these codes and is there a need for a specific ICD code for HE?"	identify this as a topic for a research recommendation.
Norgine	FULL	15	20	Norgine recommends a new research question to ensure that all patients at risk of HE are identified correctly and managed appropriately. Norgine is aware that patients with HE are often misdiagnosed and not referred for specialist care. The new research question proposed is*" Of the inexpensive commercially available tests, which one(s) are sensitive and specific enough to identify patients with HE?"*. In addition recommendations should be made regarding the setting in which the tests can be performed (primary care versus secondary care) and which clinical group could perform them reliably.	Thank you for your comment. Research recommendations are based on key uncertainties identified through the evidence reviews that are likely to inform decision-making and, as such, the GDG did not identify this as a topic for a research recommendation.
Norgine	FULL	16	9	Chapter 2 misses the opportunity to fully describe cirrhosis and its major complications, Norgine therefore recommend the following text to be added at the end of line 9. *"This is partially due to complications of cirrhosis and its management, however, to ensure continuity of care, measures for tracking and identifying high risk patients need to be implemented especially when patients attend different hospitals or are referred back to their GP. This will reduce potential for misdiagnosis and mismanagement of patients with cirrhosis as highlighted in the NCEPOD report 2013."*	Thank you for your comment. We do not feel that this addition is required, in what is intended to be a brief introduction to the chapter.
Norgine	FULL	16	17	Norgine suggest that the guideline should highlight the opportunity of identifying patients at risk of cirrhosis, as described by the NCEPOD Report (NCEPOD Report 2013. *Available from: http://www.ncepod.org.uk/2013report1/downloads/MeasuringTheUnits_FullReport.pdf*). We therefore recommend adding the following statement to end of line 17 *"Better recognition of individuals at risk of cirrhosis would allow for more timely intervention as highlighted in the key findings from the NCEPOD Report in which 71% of patients had a previous admission to hospital in the 2 years prior to their final admission and 62% of patients who had a previous admission to hospital, had an admission in which ARLD was diagnosed."*	Thank you for your comment. We do not feel that this report is relevant to this particular sentence, in what is intended to be a brief introduction to the guideline.
Norgine	FULL	16	46	Norgine believes that the information within this paragraph is incomplete and should be enhanced to cover all complications of cirrhosis. To address this, Norgine recommend the addition of the following: *"*…..antibiotics for the primary prevention of spontaneous bacterial peritonitis in those at high risk *and prophylactic treatment of patients at risk of recurrent episodes of HE".*	Thank you for your comment. We are unable to include the addition suggested as no recommendation is made by this guideline on prophylactic treatment of patients at risk of recurrent episodes of hepatic encephalopathy.
Norgine	FULL	18	General	The proposed breadth for the Clinical Guideline for Cirrhosis is currently too restrictive and in Norgine's opinion incomplete as it ignores the prevention of recurrence of HE, a major complication for patients with cirrhosis. Norgine feel this is an omission and does not correlate to the benchmark indicators highlighted in section 3.1 (incomplete guidance that partially addresses the overall objectives). Norgine therefore recommend that all the major complications of cirrhosis are included within the clinical guideline to ensure patient treatment and management is clear for both secondary and primary care clinicians. This will ensure patients are appropriately referred to secondary or tertiary care and management is clear at all levels.	Thank you for your comment. NICE guidelines are not intended to be comprehensive. The GDG was tasked with prioritising areas for evidence reviews. In particular, recurrence of chronic overt hepatic encephalopathy is already covered by NICE TA337.
Norgine	FULL	19	22	Norgine believes that within both line 22 of the guideline and section 4.3.1(e) of Appendix A, one of the major complications of cirrhosis, HE has been omitted. Norgine therefore recommend the following update to both line 22 and Appendix A section 4.3.1(e): Suggest rewording to: *"management of complications such as ascites, prevention of SBP, HE and hepatorenal syndrome".*	Thank you for your comment. The guideline scope was previously consulted on and published. We are unable to change the content of the scope at this stage.
Norgine	FULL	19	23	Norgine believes that the guideline should represent a broad and consistent approach to management of cirrhosis and its major complications and therefore suggest the wording after "tertiary care" to be amended *to "This guideline provides a broad and consistent approach to diagnosis and management of cirrhosis and its complications."*	Thank you for your comment. The sentence referred to summarises the contents of the scope in Appendix A. We are therefore unable to change the wording of this sentence.
Norgine	FULL	25	Chapter 15	Within table 4.1, chapter 15, in the "important outcomes section" Norgine feel that key measures are missing. Norgine recommends the inclusion of *length of stay and re-admission rates* to this section as these are important outcome measures which will demonstrate benefits to patients, the NHS, and commissioners. To facilitate this process appropriate and consistent coding of all major complications will be required (see comment 12)	Thank you for your comment. The GDG chose the outcomes that it felt to be most important for each of the review protocols. In this review, the outcome was worded as 'time to discharge' rather than 'length of stay'. An outcome of 're-admission' would not be relevant for a review question looking at the management of an acute episode of hepatic encephalopathy. Re-admission due to another episode of acute hepatic encephalopathy

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					would not be a continuation of the first episode, which this review question looked at solely. Treatment failure is covered by the other critical outcomes.
Norgine	FULL	235	13	Norgine believes that consistency in terminology should to be applied throughout the guideline and therefore suggest amending line 13 to *"Clinically diagnosed hepatic encephalopathy…."*	Thank you for your comment. We believe that the existing wording of this sentence is clear.
Norgine	FULL	235	17	Norgine recommends the following wording from TA337 be added: *"Expert clinical opinion suggests that people may continue to use rifaximin until death or until they have a liver transplant "*. This will aid clinicians to better manage the on-going condition and highlights the need for continuous treatment.	Thank you for your comment. We do not believe that the inclusion of this sentence is necessary in what is intended to be a brief introduction to the chapter.
Norgine	FULL	235	27	The terminology needs to be consistent so that there is no confusion, Norgine therefore suggest an amendment to line 27 to *" … the treatment of covert hepatic encephalopathy"*	Thank you for your comment. It is acknowledged that the classification of the neuropsychiatric complications of cirrhosis is considered unsatisfactory and alternative classifications have been suggested. However, these have not met with universal approval or acceptance. At present, patients with cirrhosis are classified as neuropsychiatrically unimpaired or as having minimal or overt hepatic encephalopathy. Patients with minimal hepatic encephalopathy have no neuro-psychiatric symptoms or signs but show impaired performance on neuropsychometric testing. Patients with overt hepatic encephalopathy have clinically apparent symptoms and signs which are traditionally graded, in relation to severity, on a scale of Grade I (least) to Grade IV (worst). The most recently proposed classification system employs the terms 'covert' and 'overt' but these terms do not directly relate to the terms currently in use. Thus, 'covert' refers to a new proposed grouping of minimal plus Grade I overt hepatic encephalopathy while 'overt' in the new system refers to Grades II-IV overt hepatic encephalopathy in the current system. Recent publications have confirmed that patients classified as covert behave as two distinct populations which may well have differing clinical needs. For this reason we have decided to use the conventional classification.
Norgine	FULL	235	28	Norgine feels that the terminology needs to be consistent so that there is no confusion, Norgine therefore suggest an amendment to line 27 to *" Overt hepatic encephalopathy……"*	Thank you for your comment. We believe this comment is a duplicate, submitted in error. This wording has not been amended for the reasons described in our response to ID102.
Norgine	FULL	236	34	Within section 15.2, table 93 Norgine feels that the licensed or unlicensed status of medicines recommended in the guideline be made explicit for patient safety. A number of medicines listed under Oral non-absorbable antibiotics (individual drug level, not combined within class) are either not currently licensed for use in acute encephalopathy or do not have a UK product licence (e.g. l-ornithine-l-aspartate (LOLA)).	Thank you for your comment. It is NICE policy to provide this level of information for drugs recommended by the guideline. While the GDG notes that no drugs are licensed specifically for acute hepatic encephalopathy, this guideline does not recommend any drugs for the treatment of acute hepatic encephalopathy, and so that level of information was not included.
Norgine	FULL	236	34	Within section 15.2, table 93 Norgine feels that the outcome measures should be consistent with those quoted within table 4.1, chapter 15 of the clinical guideline. Norgine therefore recommend that in the outcomes section, and in particular the important outcomes section, length of stay and re-admission rates are included as indicators.	Thank you for your comment. The 2 tables being compared (Table 1 and Table 93) are consistent in their listing of outcomes for the acute hepatic encephalopathy review.

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					The outcomes are not consistent across the different chapters, because each review question used its own research protocol.
Norgine	FULL	263	15	As part of the clinical review of this section Norgine feels that length of stay analysis is an important measure which requires highlighting. Reduction in length of stay will enable appropriate resource utilisation within secondary or tertiary care. In this respect, the utility of rifaximin-α has been demonstrated by TA337 in conjunction with a non-absorbable disaccharide.	Thank you for your comment. In this review, the outcome was worded as 'time to discharge' rather than 'length of stay'.
Norgine	FULL	264	3	Norgine are in agreement with the recommendations which refer to TA337 for the recurrence of episodes of overt HE which should be highlighted as part of the this guideline to inform clinicians on the on-going management of these patients.	Thank you for your comment. As you note, this reference to TA337 is included in the full guideline and NICE pathway.
Norgine	FULL	264	3	In the recommendation section it *states "For guidance on the prevention of recurrence of episodes of overt hepatic encephalopathy see Rifaximin for preventing episodes of overt hepatic encephalopathy (NICE TA337)."* Norgine feels that there should be some context to this statement for clinicians, and therefore recommend a separate section entitled "Prevention of recurrence of HE beyond the acute phase", including advice on identification of patients at risk of recurrent HE as well as referral pathways and ongoing management which should refer to TA337.	Thank you for your comment. The reference to TA337 has now been moved to the end of the chapter introduction on page 237, where it is more appropriate.
Norgine	FULL	265	3	Within the trade-off between clinical benefit and harm section of this guideline Norgine feels that there needs to be consistency with all treatment options when highlighting UK licencing. LOLA is not licensed or registered for use in the UK and this needs to be stated at the start of the summary for LOLA. Suggested wording would be*:" LOLA is not licensed in the UK however is used occasionally to treat an episode of acute hepatic encephalopathy and is used by tertiary care and specialist centres. Its availability outside these centres is limited."*	Thank you for your comment. It is NICE policy to provide this level of information for drugs recommended by the guideline. However, this guideline does not recommend any agent for the treatment of acute hepatic encephalopathy. The GDG notes that LOLA is not categorised as a drug in the UK and so is not subject to drug licensing.
Norgine	FULL	265	3	On paragraph 4 line 3 the current UK licence indication quoted is incorrect please amend to " Rifaximin-α is currently licensed in the UK for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age". In the pivotal study, 91% of the patients were using concomitant lactulose (see section 4.1 of the SmPC for TARGAXAN).	Thank you for your comment. The wording in this sentence has been amended from 'licensed' to 'recommended' to be consistent with NICE TA337.
Norgine	FULL	266	3	Within the other consideration section of the guideline, line 2, we recommend the following amendment to ensure consistency within the guideline. The suggested change is *" treatment of overt or covert hepatic encephalopathy,….."*	Thank you for your comment. It is acknowledged that the classification of the neuropsychiatric complications of cirrhosis is considered unsatisfactory and alternative classifications have been suggested. However, these have not met with universal approval or acceptance. At present, patients with cirrhosis are classified as neuropsychiatrically unimpaired or as having minimal or overt hepatic encephalopathy. Patients with minimal hepatic encephalopathy have no neuro-psychiatric symptoms or signs but show impaired performance on neuropsychometric testing. Patients with overt hepatic encephalopathy have clinically apparent symptoms and signs which are traditionally graded, in relation to severity, on a scale of Grade I (least) to Grade IV (worst). The most recently proposed classification system employs the terms 'covert' and 'overt' but these terms do not directly relate to the terms currently in use. Thus, 'covert' refers to a new proposed grouping of minimal plus Grade I

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					overt hepatic encephalopathy while 'overt' in the new system refers to Grades II-IV overt hepatic encephalopathy in the current system. Recent publications have confirmed that patients classified as covert behave as two distinct populations which may well have differing clinical needs. For this reason we have decided to use the conventional classification.
Norgine	Cirrhosis model	General	General	Norgine would like to thank NICE and the guidelines committee for highlighting the need for a full appraisal of Cirrhosis. The cirrhosis cost model attempts to represent the natural history of the disease, from compensated cirrhosis without varices to the development of varices (which may lead to bleeding), HCC and other decompensation events, and finally to a post-liver transplant state or to death. Norgine would like to highlight that the cirrhosis guideline and cost effectiveness model are both incomplete as they do not review or make recommendation on all of the major complications of cirrhosis including longer term management of Hepatic Encephalopathy (HE) and portal hypertension, other than in the context of varices, which were not explicitly excluded at the scoping stage of the process (see scoping document for reference).	Thank you for your comment. Whilst not being certain was is meant by 'a full appraisal', NICE guidelines focus on areas of uncertainty or variability in practice. The issues identified in the scope have been fully considered. The economic model attempts to represent the natural history of the disease in sufficient detail to answer the relevant review questions prioritised in the guideline. It does not seek to represent all complications of liver disease in detail. The effects of all the complications of cirrhosis are however included in the model through the combined total risks of death or transplant and the total cost of treatment for people with decompensated cirrhosis; but these are not separated by complication as that was not necessary to answer the questions of particular interest.
Norgine	Cirrhosis model	General		Within appendix N and the cost effectiveness model, they consider a lifetime horizon for people aged 50 years at the start of the model and with one of the 4 causes of cirrhosis (hepatitis B, hepatitis C, alcohol related liver disease, non-alcoholic fatty liver disease). The model does not include hepatic encephalopathy, a major complication for cirrhosis. Norgine feel that this is an omission which is misleading and inconsistent with the full clinical guidelines identified by the GDG and therefore request cost model covers all major complications of cirrhosis.	The guideline did not include any research questions related to chronic hepatic encephalopathy. Acute hepatic encephalopathy was examined, but insufficient clinical evidence was identified. Therefore hepatic encephalopathy was not included as a separate complication in the model (although the costs of treatment and the risks of death from hepatic encephalopathy contributed to the total costs of treatment and total risks of liver-related death for people with decompensated cirrhosis).
Norgine	Cirrhosis model	Control panel		Within the control panel worksheet it is not clear where some of the parameter estimates have been derived from, notably aetiology estimates for the beginning cohort. Norgine recommend greater clarity so that users are clear on these estimates and how they have been derived.	All sources were given in Appendix N, but more information has now also been added to the relevant worksheet of the model. It is recommended to read Appendix N when using the model for full explanation of the model design.
Norgine	Cirrhosis model	Control panel		Within the control panel worksheet both proportions and prevalence for the complications of cirrhosis have been included. The NICE clinical guideline covers all major complications of cirrhosis and as both HE and portal hypertension are missing Norgine would recommend that the prevalence of HE and portal hypertension are included so that the cost model is aligned to the NICE Clinical Guideline for Cirrhosis.	NICE guidelines are not intended to be comprehensive and this guideline does not cover all complications of cirrhosis. The economic model was designed to address those questions within the guideline selected by the GDG as currently being of greatest economic importance. Hepatic encephalopathy and portal hypertension are not modelled separately in the model, and so data for these conditions are not recorded.

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					The effects of all the complications of cirrhosis are however included in the model through the combined total risks of death or transplant and the total cost of treatment for people with decompensated cirrhosis; but these are not separated by complication as that was not necessary to answer the questions of particular interest.
Norgine	Cirrhosis model	Cost panel		Within the costs worksheet the term "increase complication costs" is confusing, specifically when costing decompensated cirrhosis within alcoholic liver disease. It is not clear whether this is just an assumed 50% premium for complication costs. It currently states that complication costs are sourced from a HTA on HCV patients (Wright 2006) which could be slightly outdated. Norgine would like better clarity to ensure users are able to understand the assumptions being used and that more up to date references are included in the model.	Thank you for your comment. The costs used for treating people with ALD for decompensated cirrhosis are higher than for other populations, due to the greater number and severity of complications in this population, as agreed by the GDG. This is explained in Appendix N. All data used in the model were taken from the best available sources, and are explained in Appendix N.
Norgine	Cirrhosis model	State cost panel		Within the state cost worksheet HE has not been included as stated above in lines 2 and 4. Norgine would recommend the inclusion of the following state costs for HE Fibrosis F3 Compensated cirrhosis Decompensated cirrhosis HCC Liver transplant - Year 1 Liver transplant - Year 2 Post liver transplant	Thank you for your comment. The economic model does not include hepatic encephalopathy as a separate complication, and so additional health state costs are not required.
Royal College of Physicians				We would like to formally endorse the response submitted by the British Society for Gastroenterology.	Thank you for your comment.

Sebastiani, G., D. Tempesta, G. Fattovich, L. Castera, P. Halfon, M. Bourliere, F. Noventa, P. Angeli, A. Saggioro and A. Alberti (2010). "Prediction of oesophageal varices in hepatic cirrhosis by simple serum non-invasive markers: Results of a multicenter, large-scale study." Journal of hepatology **53**(4): 630-638.