SeHCAT (tauroselcholic [75 selenium] acid) for the investigation of diarrhoea due to bile acid malabsorption

Diagnostics Assessment Report (DAR) - Comments

Responder reference no.	Comment no.	Page no.	Section no.	Comment	EAG Response
1	1.			1. Throughout this paper, it is suggested that "patients with undiagnosed BAM are likely to present with chronic diarrhoea". This is a fundamental error which is repeated continually in the literature and is simply not correct. Patients with BAM MAY present with chronic diarrhoea, but MUCH more common is to present with erratic bowel function which sometimes is loose / diarrhoea. Some patients actually have episodes of constipation between the diarrhoea episodes.	This was reported in the scope and as stated here "repeated continually in the literature". We do not know who made this comment; therefore we are not sure who to believe. We will change the sentence to: "patients with undiagnosed BAM may present with chronic diarrhoea" in the HTA monograph.
2	2.		General	I have reviewed this report by Kleijnen Systematic Reviews in detail. While there is evidence of a great deal of good work reviewing a large number of papers, my principal comment and regret is that the evidence reported is distorted by the introduction of new objectives that did not result from the scoping meeting, and for which we were aware there is little formal documentation. The economic analysis in my opinion should have been to look at the costs of failing to diagnose bile acid malabsorption when a SeHCAT test is not performed	The economic analysis did look at the costs of failing to diagnose bile acid malabsorption when a SeHCAT test is not performed. However, most of the model inputs were based on expert opinion as there were no data. If the commentator is alluding to the issue of extra tests that is raised at comment no 3. please see our response there.

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3	3.			We feel that the significant issue in this review for NICE is the failure to fully ascertain the benefit of an accurate diagnosis of BAM in chronic diarrhoea/IBS and to appreciate the 'size' of this problem. We consider that to base subsequent recommendations regarding the diagnostic method of choice on therapeutic outcomes or rather lack of (or relative lack of) such outcomes fails to recognise the potential burden of this disease. We consider that the focus of the rest of the review process should be to evaluate the considerable literature which suggests a failure to diagnose this condition leads to a significant symptom burden for patients and increased number of potentially expensive and unnecessary diagnostic tests	'Significant symptom burden' arising from failure to diagnose BAM is directly related to the effectiveness (or otherwise) of treatments – if there is no effective treatment for a disease then there can be no improvement in symptom burden consequent upon its diagnosis. Thus evidence for the availability of an effective treatment is essential to the relevance of any evaluation of test performance. However, we do acknowledge that the usual approach to cost-effectiveness studies are somewhat limited when applied to diagnostic assessments as there may indeed be non-health related benefits to testing. However, currently no methodology exists to take these issues into account. Regarding the avoidance of additional tests, the care pathway described in the scope does not include any additional tests (once patients have entered the arm for functional disease), celiac serology already having been undertaken, neither does it include an option for patients to re-enter the investigation arm for functional disease.

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					Evidence from an existing systematic review (Cash et al.) suggests that the prevalence of organic disease (with the exception of celiac) in the IBS population is similar to that in the general population (<1%); further aggressive investigation, with the aim of detecting organic disease, would therefore seem difficult to justify. We are unclear what additional investigations the reviewer feels could be avoided. We also considered that inclusion of further testing in treatment non-responders would require evidence about the accuracy of these additional tests, information on which treatments are available once test results are known and information on the response rate to these treatments. Additionally, it is important to realize that such testing would probably be done both in the no SeHCAT strategy for treatment non-responders and in the SeHCAT strategy in the test-negative patients with non-response. Thus, the incremental effect of including such additional tests would be limited.

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1	4.	12	1.1	"In consultation with NICE and clinical experts during early scoping it was agreed that the review should focus on two populations". This is a shame and it is difficult to understand why this decision was made. While BAM misdiagnosed as IBS constitutes a very large number of patients, there are other large populations of patients who have been excluded as "irrelevant" by this narrow approach and who have undiagnosed BAM. These populations itotal substantially more patients than those with Crohn's and include: Post cholecystectomy diarrhoea, during pelvic radiotherapy, after pelvic radiotherapy, post right hemicolectomy diarrhoea, after pancreatitis, after vagotomy, diabetics, those with microscopic colitis etc. At the very least, this report should acknowledge that these groups are large and this exercise perhaps made a mistake in excluding these other populations. . During and after pelvic radiotherapy, in particular, there are excellence incidence and prevalence data in many published studies.	This is a question for NICE. However, most of the groups mentioned here do not have chronic diarrhoea with unknown cause; therefore, these populations do not fulfil the inclusion criteria for this review.

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2	5.	13	1.1	This should be "there is no *commercially available* comparator for this diagnostic test." Measurement of 7α-OH 4-cholestenone (C4) is available in specialist referral labs. C14-glycocholic breath test and faecal bile acid measurements were used to validate the test originally (see below).	We have seen studies trying to establish the validity of other methods to assess BAM using SeHCAT as the reference standard. We have seen no studies using other tests then SeHCAT as the reference standard. In the literature it is generally accepted that these other tests do not measure bile acid malabsorbtion. Furthermore the scope states: “The serum 7-alpha-hydroxy-4-cholesten-3-one test may be an alternative technology within this assessment. However it is currently only available in specialist centres or as a research procedure and will therefore, not be included in the evaluation.”
2	6.	13	1.1	"…variety of other diagnostic tests". The clinical and economic problem is that numerous other expensive tests are often performed to establish one of the other possible diagnoses (CT, MRI, capsule enteroscopy, motility measurements, hormonal studies etc.) if a definitive diagnosis of BA malabsorption/diarrhoea is not made. These should be included in this summary.	This was extensively discussed at the scoping workshop. The clinical experts did not rule out the possibility that other tests might still be necessary, even after a positive SeHCAT test. Therefore, there are no costs saved in this respect. This was the reason why the current study was limited to patients clearly distinguished as having functional disease. Regarding the issue of additional tests in non-responders in this population,

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					see comment 3.
2	7.	13	1.1	It is correct to note a trial of treatment (without definite diagnosis by SeHCAT) is not widely used in current practice.	No response required.
2	8.	14	1.1	The BSG Guidelines date from 2003 and are currently being revised.	No response required.
2	9.	14	1.2	I am most concerned that the reviewers have "translated" the agreed areas in the final scope into two additional questions (2 and 3). It was agreed that as insufficient data existed regarding trials of sequestrants, this would not be part of the review. Yet this will feature at length on subsequent pages. The review team have produced no analysis of the costs and yields of other tests which may be undertaken in the absence of a positive diagnosis of BAM, nor of the disutility of failing to make the correct diagnosis and to continue with non-specific treatment for IBS-D or with expensive agents in Crohn's.	Regarding the inclusion of ToT in some of the analyses: the scoping document states: “The main comparator for the assessment will be tests and clinical observations contained in the BSG guidelines for the investigation of chronic diarrhoea.” And the BSG guideline states: “In the absence of these diagnostic tests, a therapeutic trial of cholestyramine is sometimes employed, although the value of this approach has not been the subject of study.” Therefore, ToT is clearly included in the scope. We considered it of value to the committee to have results for both options (with and without ToT as a comparator).

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					The effectiveness of treatments following a diagnostic test should always be part of the decision to use a diagnostic test. Whilst the health economic study does not include potential additional tests to be done once patients do not respond to IBS-D treatment (see comment 3), the analysis does take into account the impact of not diagnosing patients with BAM on treatment costs and health related quality of life.
4	10.	14	1.2	Research question 1 does not accurately reflect what SeHCAT is about. The question is 'what are the effects of SeHCAT compared to no SeHCAT in terms of chronic diarrhoea, other health outcomes and costs? We would ask the Committee to remember that SeHCAT is a diagnostic test and does not in itself impact on diarrhoea, it rather allows the clinician to provide a diagnosis and therefore better decide on the most appropriate treatment, with resultant implications on health outcomes and costs. This is an important differentiation that needs to be remembered.	It is not clear which other health outcomes should have been included here. Our economic analysis takes all these additional implications into account. Also see our response at comment no. 3.
2	11.	15	1.3	Focussing on only 3 studies is surprising (and probably incorrect) and will be addressed later.	Response follows

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2	12.	15	1.3	There are many studies which can be pooled as shown below where patients diagnosed at different SeHCAT cut-offs are treated.	Response follows
4	13.	15	1.3	The assessment group note that there is data available to distinguish 3 different SeHCAT cut-off points. We feel it is important for the Committee and Assessment Group to understand that there is no single cut-off point recommended by GE HC because it is felt that the range of retention scores add value to the clinician for decision making. The retention score alongside the clinical symptoms presented allow the clinician to form a picture and better inform their treatment decision. Generally, a 7-day SeHCAT retention value greater than 15% is considered to be normal, with values less than 15% signifying excessive bile acid loss as found in BAM. A retention of between, 0 – 5% is considered to be indicative of severe BAM, 5 – 10% moderate BAM and 10 – 15% mild BAM. Such indications of severity guide the clinician in determining the appropriate treatment. Lower retention scores indicative of severe BAM help the clinician quickly define the correct dosage of BAS for the individual patient, while for other patients with mild BAM the clinician might decide diet-modification only is required (something that has	Since no studies are available on the impact of diet modifications on BAM, this was not considered as part of the economic evaluation. Except for diet advise, no other treatment than BAS is available. So after having classified a patient as either mild, moderate or severe, a decision needs to be made on who receives BAS. And at that point, 3 options are available to clinicians: all patients, only moderate and severe, or only severe. To inform this decision, the current analyses offer information about the cost-effectiveness of SeHCAT for various cut-off points.

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				not been reflected as an option within the current analyses).	
2	14.	16	1.3	See above. It is a major flaw of this review that clinical expertise has been misinterpreted so far.	
4	15.	16	1.3	The assessment group state that trial of treatment (ToT) could not be completely excluded as an option for a comparator. We strongly disagree with this statement as ToT is not routine standard practice in the NHS and is not identified as a comparator within the scoping document for this evaluation. The question for consideration is the use of SeHCAT as a diagnostic option compared to current routine patient pathway (currently clinical observation and tests contained in the BSG as stated). ToT may have previously been used as a last resort to treat symptoms but it is not a recognised diagnostic option therefore we request that the Committee ignore the analyses presented in this report which include ToT as a comparator arm.	This is for the committee to decide.
4	16.	16	1.3	We would like to bring to the attention of the Committee that within the 3rd model developed by the assessment group there are no additional diagnostic tests considered in the costing but only the regular treatment of IBS-D. Clinical experience suggests that	See comment 3 regarding additional testing and comment 23 regarding diet advice for BAM.

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				long-term sufferers of chronic diarrhoea often have repeated tests over a period of years which must be recognised within the long-term model (please see supporting document: Additional References). While an initial round of testing for organic disease may have been completed before a diagnosis of IBS-D, it is likely that for those patients who do not respond to IBS-D treatment, repeat testing such as colonoscopy will be considered to ensure nothing has been missed in the initial diagnostic assessment. This will have implications on the cost-effectiveness analyses as the mean cost of the IBS-D non-responders will increase. Comparatively for those patients with a BAM diagnosis clinical experience suggests that at least some improvement is found for all patients given the right BAS provided at the correct dose and/or dietary modifications. It should also be noted that as some patients with a confirmed diagnosis of BAM can be treated successfully with dietary modifications this will also have implications on the cost-effectiveness analyses, the SeHCAT arm should become less expensive as there is no longer a need for daily BAS treatment for all patients.	
2	17.	17	1.4	The value of BA sequestrants in Crohn's had been established in studies in the late 1960's and early 1970's which predated SeHCAT. These used	No response required – Information for the committee.

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				alternative technologies, mostly not currently available. The ethics now of treating patients without an abnormal (SeHCAT) test with a poorly tolerated drug, and not with another effective agent, are unlikely to be acceptable – hence the lack of data.	
2	18.	17	1.4	It is unfortunate that attempts at a life-time economic analysis could not be done. There are data on the lack of change of SeHCAT over many years, the number of extra tests performed before BAM is diagnosed, and the lifelong effects of IBS treated non-specifically.	We agree that it is unfortunate that the life time analyses are very limited and uncertain. As is presented in the report, there are a few studies that give some indication about long term effects but these are very limited, do not allow the calculation of transition probabilities and often present conflicting information.
4	19.	17	1.4	We would request the Committee consider that the primary purpose of SeHCAT is not to predict the response of treatment with BAS but to provide a diagnosis of BAM. The ability to predict the response to BAS is a valuable addition to the diagnostic abilities of the test as it can guide the titration of BAS which can facilitate better compliance. Especially as patients can be reluctant to persevere with BAS treatment, the ability to quickly titrate the dose appropriately to gauge a response is a valuable tool for the clinician.	No response required – Information for the committee.

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4	20.	17	1.4	We would suggest to the Committee that the cost-effectiveness results of the ToT comparison are irrelevant for this evaluation as ToT is not routine practice, it is not a recognised option for the diagnosis of BAM and was not identified within the scoping process as either a comparative or alternative technology.	No response required – Information for the committee.
2	21.	18	1.4	Trial of treatment is being used as a comparator for almost a page of this Executive Summary. As stated above (and in the document), there are no data to justify this extensive analysis. A Pubmed search on "trial AND "bile acid sequestrant" AND diarrhea" produces only ONE paper (which used C4 for diagnosis in 4/24).	No response required – Information for the committee.
4	22.	18	1.4	While we recognise that the longer-term modelling is challenging due to a lack of data to inform transition probabilities it should be noted that for both populations SeHCAT 15% appears within the acceptable threshold of cost-effectiveness. This is important given that clinically, SeHCAT is currently the only easy way to diagnose BAM. Taking into account the potential cost-offsets from avoided tests (see comment 40) and potential improved QoL from earlier diagnosis and appropriate treatment we feel that these results will only improve as more evidence becomes	As mentioned previously, during the scoping workshop the clinical experts could not rule out the possibility that alternative tests might still be necessary after a positive SeHCAT test. We are not aware if any evidence for the effectiveness of diets or improvements in QoL from earlier diagnosis and treatment. See also comment 16.

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				available. It is also feasible that some patients can be successfully managed through diet rather than BAS at minimal longer-term cost which is not reflected in the longer-term model and could again improve the cost-effectiveness of SeHCAT.	
1	23.		1.5	The published literature on BAM fundamentally fails to define the nature of optimal treatment for bile acid malabsorption and as such, as the authors have not understood this, this systematic review has a significant problem and it has not taken into account the role of low fat diet in managing people with BAM> BAM causes symptoms when there is more fat and hence more bile in the diet. SeHCAT scanning has the ability to define with considerable accuracy a population who can often be managed with diet alone (SeHCAT 10-15%) and a population who need bile acid sequestrants (5-10%) and a population who often need both (0-5% SEHCAT). This is particularly important when the available bile acid sequestrants are less than optimal (cholestyramine poorly toerated and ineffective if there is steatorrhoea), colesevelam (very large tablets and expensive). The possibility of managing patients with no medication and using a low fat diet is not even mentioned in this review. This is hardly surprising as	Our review focussed on the treatment with BAS, as this was the only treatment option described in the scope. However, for the HE model we tried to find evidence about the effectiveness of diet for BAM but did not find data It should be realized that the results of the HE analysis are mainly driven by the relatively high cost of the SeHCAT test itself. So by replacing the BAS medication with diet advice, the SeHCAT strategies will become less costly, but still more expensive than the no SeHCAT strategies. At the same time, the effectiveness may be lower than that of BAS, potentially leading to a reduced number of responders in the SeHCAT strategies. Overall the impact of including diet may be expected to be limited.

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				this approach to the therapy is not explored in the literature adequately, and as there is so little UK expertise in managing large groups of patients, these subtleties are rarely discussed or taught. However, it makes the cost effectiveness analysis as has been attempted here rather difficult to believe! It is a pity that more effort was not made to identify those with clinical expertise in this field ie those ordering large number of SeHCAT scans - rather than relying on the scanty published data?	
4	24.	18	1.5	We would like to emphasise to the Committee that while there is heterogeneity in study design and small patient numbers, there is a very consistent and clear message that SeHCAT can diagnose BAM with high sensitivity and specificity. The cut-offs identified can be used by the clinician to help guide the dose of subsequent BAS and should not distract from the evaluation of SeHCAT as a diagnostic tool for BAM (see comments 13 and 19)	No response required.
2	25.	19	1.5	This section on "Conclusions" repeats findings of the Results in some detail, again focussing inappropriately on response to treatment. (See point 6).	No response required.

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2	26.	19	1.5	To mention "uterine cramps" again is but one example of the lack of awareness and balance in this report. Abdominal cramps, but not uterine cramps, are commoner with colesevelam (ref 47).	The report states that there are no significant differences in any of the adverse events. The exact data are report on page 61, table 7.
4	27.	19	1.5	One particular RCT is noted in patients with IBS-D comparing treatment with BAS to placebo with no significant differences noted. We would suggest that this is exactly why SeHCAT is required so that BAS is correctly given to patients with a diagnosis of BAM and also the dosage can be appropriately titrated given the severity of BAM indicated by the retention score thereby improving the likelihood of patient response. Obviously patient numbers in this study are small but if we also look at Fernandez-Banares (Am J Gastro, 2007; 102: 2520 – 2528; Systematic Evaluation of the Causes of Chronic Watery Diarrhoea with Functional Characteristics), from 62 patients with watery diarrhoea only 20% (12 patients) actually remained without a specific diagnosis. 45% of the patients were actually diagnosed with BAM. Also of significance to this discussion was that once correctly diagnosed, diarrhoea was stopped for all patients without relapse at 12 months given specific treatment measures appropriate for the diagnosis. This reflects the potential value of a diagnosis and subsequent	As reported on page 59: “All participants had fasting plasma 7alpha-C4 (C4) measured to assess for underlying bile acid malabsorption and had serum FGF-19 measured. However, it is not certain whether this was used as an inclusion criterion. SeHCAT was not used in this trial.”

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				appropriate treatment.	
4	28.	19	1.5	Trial of treatment is not an appropriate comparator for consideration in this evaluation.	No response required – Information for the committee.
2	29.	20	1.6	The definitions of "positive SeHCAT" are semantic and not relevant. Most people accept mild, moderate and severe for 15%, 10% and 5%, but it is a continuous spectrum where many other factors lead to the symptoms of diarrhoea.	No response required – Information for the committee.
2	30.	20	1.6	These study designs are appropriate and informative and will give conclusive results acceptable to modern standards of review. However the reviewers have ignored that much of the data to support SeHCAT as a diagnostic agent came from studies performed to the then acceptable standards in the 1980's and 1990's.	We assessed SeHCAT against current standards, and our report concludes that the data to support SeHCAT as a diagnostic agent are not acceptable to current standards.
4	31.	20	1.6	We agree that additional research would provide further clarity on this research question however we would urge the Committee to consider key facts around SeHCAT. SeHCAT is the only diagnostic test easily available for BAM with high sensitivity and specificity.	No response required – Information for the committee.

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				Chronic diarrhoea is a significant health burden both in economic and quality of life terms therefore the ability to provide a diagnosis and facilitate appropriate treatment is of significant value to both the patient and the NHS.	
4	32.	23	2.1.2	It is noted that people with chronic diarrhoea are often diagnosed as having IBS-D if a definitive cause has not been identified. We would ask the Committee to seriously considered this point – many people are diagnosed as IBS-D as a default diagnosis. This is exactly what SeHCAT is designed to avoid – it can provide an accurate diagnosis of BAM and provide the clinician with further information to guide more appropriate treatment and subsequent symptom resolution/improvement. It is also noted on page 21 that IBS is often a life-long disorder. For those with a 'default' diagnosis of IBS-D it is fully conceivable that when IBS-D treatment does not resolve symptoms sufficiently as it is perhaps not an appropriate treatment, the clinician will try more tests or repeat tests such as colonoscopy in an attempt to gather more information to help the treatment decision or to ensure nothing was missed in the initial diagnostic tests. As noted in comment 16 we feel that the assumption of no repeat testing in the long-term model considerably under-estimates both the cost and	See comment 16.

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				potential discomfort (QoL) of a unresolved diagnosis of IBS-D.	
2	33.	25	2.1.3 Fig	This is not a good representation of the data in the references quoted. These figures are taken from different reviews. IBS (3) needs to be bigger than Crohn's (4) and the proportions in group 5 and 6 should be bigger.	The size of the circles are indeed not to scale. The estimated size of each population is presented in the legend under the figure.
2	34.	29	3	See above (comment 14). This was not a review of treatment.	See previous response.
4	35.	29	3	Please note comment 28. We would ask the Committee to remember that SeHCAT is a diagnostic test and does not in itself impact on diarrhoea, it rather allows the clinician to better decide on the most appropriate treatment of the chronic diarrhoea, with resultant implications on health outcomes and costs. This is an important differentiation that needs to be remembered.	See previous response.
4	36.	37/38	4.5	It should be recognised that SeHCAT has been on the market for a long time and the evidence requirement 20 years ago was very different than today. While there is therefore no specific gauge accuracy for SeHCAT and a need to use the treatment response as	The studies mentioned here were assessed for the review, but excluded for the following reasons: - Notghi – This is a review, no original data.

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				a reference, we would ask the Committee to keep in mind the high sensitivity and specificity results noted for SeHCAT. We would also direct the Committee's attention to the Notghi paper (Nuclear Medicine Communication, 2011 (32): 960 – 966) and the Nyhlin et al. paper (Gastroenterology 1983:84; 63-68). Both of these papers, amongst others have reported that seHCAT has been validated and also highlights its accuracy. There are other studies that have been missed out during the process, namely Nyhlin et al (as above), Van Tilburg et al. JNM 1991 and Thaysen et al. Gut 1982.	- Nyhlin - The population did not fulfil the inclusion criteria: 45 patients including healthy controls and Crohn's disease with ileal resection. - Van Tilburg – Aim of the study was to re-evaluate the recommended reference values for the SeHCAT test, used in the analysis of chronic diarrhoea. Data were not reported in a useful way for this review (no number of pos SeHCAT at a certain cut-off) - Thaysen – The population did not fulfil the inclusion criteria: 8 patients without gastrointestinal complaints and 30 patients with various gastrointestinal disorders (no further details).
2	37.	39	4.6	Many of the key studies validating the use of SeHCAT against the previous accepted standards of C14-glycocholate excretion or faecal bile acids seem to have been missed out. These include Thaysen et al. Gut 1982; 23:862-5 (20 patients with chronic diarrhoea); Nyhlin et al. Gastroenterol 1983: 84: 63-8 (10 chronic diarrhoea, 6 non-resected Crohn's); Van Tilburg et al. J Nucl Med 1991; 32: 1219-24 (211 patients) among others.	See previous response.

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2	38.	39	4.6	Appendix 5 lists a large number of additional papers excluded in many cases for debatable reasons of "Population" or "Outcomes". Closer reading of many establishes a subgroup of relevance to this review. I would be prepared to review these further for the DAR.	Please let us know which papers do fulfil the inclusion criteria for this review as described in our protocol.
4	39.	54	4.6.1	It is noted that the effectiveness of BAS in people with chronic diarrhoea with unknown cause and in people with Crohn's disease and chronic diarrhoea of unknown cause is not known. We believe that there is sufficient evidence available that does give a good indication of the likely effectiveness of BAS. For example, Wedlake (see comment 90) and Fernandez-Banares (see comment 51). In addition, while the effectiveness of BAS is relevant to the evaluation we would ask the Committee to consider that the question is around the use of SeHCAT as a diagnostic for BAM not around the effectiveness of BAS. The uncertainty of information around BAS should not detract from the benefit that can be derived from a diagnosis of BAM for patients. In addition, some patients can be successfully managed with dietary measures after a diagnosis of BAM which would have implications for the longer-term treatment costs associated with a diagnosis of BAM, likely making the cost-effectiveness	We are not sure which papers by Wedlake and Fernandez-Banares are meant here. We believe we have assessed all relevant studies. If this refers to Wedlake 2009 (Clinical Therapeutics, pp2549-58), this study is in a very special population (cancer patients) and is a retrospective review of electronic patient records in combination with a patient questionnaire. For the effectiveness of a treatment one would ideally look at randomised controlled trials and as a minimum a control study. If this refers to Fernandez-Banares 2007 (Am J Gastroenterol, pp 2520-8), the ai of this study was to assess prospectively the presence of gluten-sensitive enteropathy, bile acid malabsorption, and sugar

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				ratios more favourable.	malabsorption in consecutive patients with chronic watery diarrhoea of obscure origin fulfilling Rome II criteria of functional disease. The study does not have a control group and does not seem to assess the effectiveness of treatment.
4	40.	54	4.6.2	It should be noted that the retention values resulting from a SeHCAT test act as a guide to the clinician on what might be the appropriate treatment option for the patient. It is conceivable for a patient to have a negative SeHCAT test with a retention score of say 18% but present with symptoms that might encourage the clinician that treatment with BAS might be appropriate. Alternatively, the clinician may note a retention score of 13% indicating mild disease and given presenting symptoms suggest dietary measures rather than BAS.	No response required – Information for the committee.
2	41.	59-61	4.6.4	SeHCAT is not used in this study – why is it included? The review is of Diagnosis, not possible treatments.	See previous responses
4	42.	73	4.7	It has been presented that the different cut-offs considered in the 3 studies used to assess the relationship between SeHCAT test and treatment with cholestyramine are perhaps a weakness. However we would suggest that they allow a more continuous	See previous responses

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				evidence base to guide clinician decision making – if BAM is identified as severe (<5%) the clinician knows they are very unlikely to be giving BAS unnecessarily (specificity 1) while conversely with a more moderate diagnosis of BAM <15%) the clinician will know that they have identified all patients with BAM who are appropriate for a trial with BAS (sensitivity 1). The information provided supports the clinical decision making process (BAS treatment, dietary modification) and also supports the efficient titration of BAS which can facilitate better patient compliance.	
2	43.	74	4.7	See comment 9. This is from the study in comment 41 and is misinterpreted.	See previous responses
2	44.	79	5.2	This is poor justification of use of Trial of treatment, ignoring evidence at the scoping meeting.	During the scoping meeting it was mentioned that according to a questionnaire send out by the BSG, at least 50% of of GE have used Trial of treatment. Also, no firm conclusions were drawn during the scoping meeting or in the final scope. Therefore it seemed prudent to present results both with and without ToT.
4	45.	79	5.2	The assessment group note that the clinical experts at the scoping meeting stated that ToT is rarely used as a treatment strategy and thus is not a relevant comparator for this evaluation. We do not understand	The scoping document mentions the ToT under comparators, without explicitly stating if it should or should not be considered as a comparator. Thus, we considered it of value

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				why the assessment group have persisted to include an analysis considering ToT as a comparator and would ask the Committee to disregard such analysis as it is not routine standard practice in the NHS, it has not been noted as a comparator in the scoping document and discussion, and is therefore not appropriate for consideration in this evaluation.	to the committee to have results for both options.
2	46.	80	5.2.1	"… no data available on the accuracy of SeHCAT" ignores much early data (comment 98 and more).	See previous responses
4	47.	80	5.2.1	It is noted that if SeHCAT is positive (retention value <15%) patients are treated with cholestyramine and they may or may not respond to that treatment. We feel that it is also important to consider the evidence on the effectiveness of colesevelam for patients who have not previously responded to cholestyramine (Wedlake et al. Effectiveness and tolerability of colesevelam hydrochloride for bile acid malabsorption in patients with cancer: a retrospective chart review and patient questionnaire. Clin Ther 2009, Nov 31 (11): 2549 – 58). Significant improvements were noted for these patients and 67% were also found to continue treatment for up to 4 years. By considering only cholestyramine, the assessment group are not reflecting the full potential response to BAS treatments possible through the correct diagnosis of BAM. In	We did not consider cholestyramine as the only treatment. However, none of the included studies assessing SeHCAT used colesevelam. The study by Wedlake mentioned here is in a very special population (cancer patients) and is a retrospective review of electronic patient records in combination with a patient questionnaire. For the effectiveness of a treatment one would ideally look at randomised controlled trials and as a minimum a control study.

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				addition, some patients with a positive BAM will not get BAS but be successfully treated with dietary modifications.	
4	48.	85	5.3.1	As noted in comment 47, we feel it is an under-reflection of the true response to BAS by only assuming treatment with cholestyramine. While there is reduced compliance with cholestyramine as noted by the assessment group, there are also alternative BASs' available that show high response rates for those who have not previously responded to cholestyramine such as colesevelam.	We found no further evidence for colesevelam.
2	49.	86	?7	The use of the expert questionnaire is problematical. The choice of questions were not validated and many of these BSG experts felt these were not accurately phrased or relevant, and were unable to answer. The response rate was only 7 out of 20.	We regret the poor response rate and that there was no time for validation of the questions. The questions were very relevant for the economic model. The fact that experts were unable to answer the questions illustrates the difficulties to properly model the cost-effectiveness of SeHCAT and the lack of evidence.
2	50.	87	5.3.1	The clinical "response" is considered too simply and rather naively. Is a partial or total response at any particularly time point meant? Is it a sustained response? Does this allow a free diet with no	Appendix 4 (page 206) describes the definitions of response as used in the individual studies. We agree that there was much variation in the definition of response

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				restrictions?	in the various studies.
4	51.	87	5.3.1	From the expert survey the assessment group have estimated that a mean of 52% of IBS-D patients will respond to IBS-D medication when no SeHCAT test is available. This is based on only 7 expert opinions which also demonstrate a huge variation in estimations including the extremes of 0 and 100%. We believe the 52% probability of response to IBS-D treatment to be overly optimistic estimate, especially, when papers such as Fernandez-Banares (Am J Gastro, 2007; 102: 2520 – 2528 – see comment 9) found that out of 62 patients with watery diarrhoea only 12 actually had functional disease. If these 62 patients had been given IBS-D medication it is unlikely that a 52% response rate would have been achieved. In addition, this assumption within the current structure of the model conveys very little chance that SeHCAT will be ever be cost-effective – there is a high, estimated response rate for IBS-D patients, IBS-D responsive patients have a higher QoL than responsive BAM patients but at a considerably reduced medication cost (IBS-D medication only £0.17 compared to £0.63 per day for BAS). Finally, we note that there is nothing in the expert survey to estimate	The Fernandez study showed a rate of positive SeHCAT test of 60% which is much higher than the pooled mean (36%, see table 18, 10% cut-off), indicating that this study is an outlier. Also, in this study 16% of patients had celiac disease, which is already excluded in our population. While we agree that the 52% response rate is extremely uncertain, given the very small sample of experts, we cannot positively state that it is an overestimation. Note that in our sensitivity analyses, we have taken the uncertainty around this point estimate into account. Repeat tests avoided – see previous response (comment 3).

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				what happens with these non-responding patients. Clinical experience suggests that it will be these non-responders that are likely to have repeat tests which could be avoided with the use of SeHCAT (see comment 16).	
2	52.	88	5.3.1	There are so many assumptions in this section that the value of it must be questionable.	We agree, the economic model is largely built on assumptions. Therefore, our main conclusion is that all strategies may be cost-effective given the current level of evidence.
4	53.	88	5.3.1	The assessment group have assumed a response rate of 28% which is varied to 21% in the scenario analyses. Could the assessment group explain why there is no higher response rate considered in the scenario analyses. This appears to be a very one-sided analyses.	Indeed normally one would vary such percentage upwards and downwards. In the PSAs we have always used a symmetrical confidence interval around either 28% or 21%. 21% was chosen for a scenario since it is the break-even point where the ToT strategy leads to the same number of responders as the SeHCAT 15% strategy. Thus, this scenario is unfavourable towards ToT. A higher response rate would be ToT favourable and make it less likely that SeHCAT is cost-effective.

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4	54.	88	5.3.1 88	The assessment group have considered 2 scenarios for BAS responders based on the impact of treatment on QoL due to IBS-D. We would argue that while this is a reasonable starting point the smaller increment as noted in scenario 2 is overly pessimistic. It has been noted that a diagnosis and treatment of BAM can be a life-changing experience for some patients (Noghti 2011). To reduce the improvement in QoL by 25% due to general unpleasantness of cholestyramine seems overly pessimistic. Furthermore, this reduction is applied for lifetime and does not consider those patients that stop treatment due to no longer needing the treatment or stopping the treatment due to various compliance issues. This has been reflected in the costs (section 5.3.4) but has not been applied to the QoL reduction. In addition, there are other BAS treatments available that are not associated with the same unpleasantness and also some patients are successfully treated with dietary modifications. Overall, we believe that the improvement on QoL will not be less than that associated with improvements due to IBS-D treatment when these other points are taken into consideration. As such, many of the scenario analyses undertaken later on in the report (scenario 1 through 7) are inappropriate.	We presented both scenarios in an effort to anticipate the questions that might arise in the diagnostic committee. If they concur with this line of reasoning, they can disregard the scenarios with the lower utility for BAS responders.

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2	55.	89	?1	The costs do not seem to include any additional or repeated tests in the patients who do not respond to IBS therapy.	See previous responses (e.g. comment 3)
4	56.	89	5.3.1 Costs	We would argue that the dosage of cholestyramine assumed per day (12g) is a high estimate to use within the economic model. The starting dose is often 4g per day and it has been noted that for many patients this is sufficient (Pattni 2009, Recent Advances in the understanding of bile acid malabsorption. British Medical Bulletin, 92: 79 - 93). The other studies noted by the assessment group also state quite lower ranges (4 – 12g) which could have significant implications on the longer-term treatment costs (daily cost of BAS currently £0.63 versus daily cost of IBS-D medication at 0.17).	As mentioned in the study report, our assumption of the dosage was based on the only study that reported the average dosage. In HE analyses, means instead of medians or modes should be used. But looking at the other studies that report some descriptive statistics about dosage, an assumption of 8g per day may have been reasonable as well. The short term results would change very little, as the costs of the SeHCAT test drive the results. In the long term models, a lower cost of BAS would have a small favourable impact on the cost of the SeHCAT strategies, but most likely only a small impact on the conclusions.
4	57.	90	5.3.1	The assessment group note 3 main types of resource use with IBS-D; medication, dietician visits and counselling. We would argue that there are additional costs that need to be considered in the model for example, repeat testing for long-term non-responders to IBS-D treatment (possibly repeat colonoscopy or sigmoidoscopy). We note that while treatment for	See comment 3 regarding additional testing. Indeed the cost estimates are highly uncertain. The only place at which we have applied a triangular distribution is for the individual responses of the experts to the question how

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				IBS-D was estimated based on expert opinion, the survey did not question about the possibility of additional diagnostic testing for long-term non-responders and we feel this is an important oversight. As noted in earlier comments, unresolves IBS-D patients are likely to be referred for repeat tests to ensure that prior diagnostic tests have simply not missed something. A diagnosis of BAM will avoid such repeat testing. The cost estimates are also based on the opinion of only 7 clinicians which given the differences in their response is unlikely to be representative of UK practice. Furthermore, we consider the handling of the uncertainty surrounding the estimates with a triangular distribution to be inappropriate as it is highly likely to severely underestimate the uncertainty in costs and provide estimates which appear misleadingly robust.	many patients would eventually respond to IBS-D treatment. For this question, experts gave a min, mean and max. We do not see why a triangular distribution for such expert opinion would severely underestimate uncertainty, as it seems likely that the experts intended the limits of the range to be less likely to represent the true response rate than the mean. For most cost estimates we have applied gamma distributions, which actually represent a very large uncertainty about the costs.
4	58.	91	5.3.1	Table 26 and Table 27 – can the assessment group confirm the period of time associated with these tables? Looking at the tables on page 100 the costs represented in Table 26 and 27 appear to be for a 6 month period. Additional clarification would help the review process.	The mean costs presented in Table 26 and Table 27 are one-off costs that occur once in the decision tree and not in the Markov model. We made this assumption since the timing of these types of costs may vary between patients.

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4	59.	94	5.3.1	Cost: It has been assumed that the cost for IBS responders is only equal to the medication costs used but from Table 26 every patient will have at least 1 visit to a dietician therefore this is an under-estimate of the costs of IBS responders as they also will have a visit to a dietician and a small percentage may have psychological treatment.	As we state in the report: In the decision tree (which represents the first 6 months) for the treatment of IBS-D, we distinguish three main types of resource use: a) medication, b) dietician visits and c) counselling and psychological therapy. All of these were estimated based on expert opinion. In the Markov model, only medication costs apply. Also note that not all patients have at least 1 dietician visit.
2	60.	97	5.3.	The large variation in expert's responses suggests these questions were not carefully framed. Again there is no evidence that alternative, further investigations were included in this economic analysis.	It is very well possible that another approach to the expert solicitation would have led to different responses. Regarding the further investigation, see our previous response (comment 3).
4	61.	98	5.3.3	As noted in comment 59 the assessment group appear to have under-estimated the costs associated with the treatment of chronic diarrhoea for non-responders as such treatment only focuses on the available medication options and does not consider visits to dietician and counselling/CBT etc. Table 32 on page 100 suggests that these costs may have been included in the Markov model but it is not clear and can hamper a review of the analyses undertaken.	See response to comment 59.

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2	62.	100-140		A lot of analysis but were the parameters appropriate?	See previous responses
4	63.	102	5.3.6	The assumption that the response to BAS in the ToT strategy of 28%, equivalent to the percentage of responders in the SeHCAT 15% strategy seems overly optimistic given that the clinician will have no indication of likely dose needed as suggested by the retention value provided by SeHCAT. Without a confirmed diagnosis to motivate the patient, the unpleasantness of cholestyramine and the inability of the clinician to start the dose titration appropriate given the severity of disease, it is likely that the response rate will be much lower.	This point is discussed in the report at various places. We explicitly asked our experts for their view on the reasoning behind the 28% and they indicated that the reasoning was reasonable. However, we also included an alternative scenario with a response rate of 21% to take these issues into account.
4	64.	102	5.3.6	There is an assumption of no difference in the number of gastroenterologist (GE) visits between the various strategies. We believe that this assumption might hold in the short term but not for longer-term modelling. For patients who do not respond to IBS-D treatment over the longer-term there are likely to be significantly more GE visits and repeat tests in an attempt to get to the roots of the problem. Clinical experience suggests that all patients diagnosed with BAM will have at least some response to treatment through a combination of using the right BAS at the correct dose and/or dietary modification. Any	We agree that maybe some differences will exist between the number of GE visits and GP visits in the various strategies. However, we have no data at all to support this, and this only adds to the overall uncertainty that exists in this economic evaluation.

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				additional symptom relief for BAM diagnosed patients will likely be managed in primary care, in contrast to the unresolved IBS-D patients who will return to the GE periodically. These repeat GE visits and possibly additional testing must be reflected in the long-term costing of the IBS-D arm along with the QoL implications of continuing diarrhoea.	
4	65.	104	5.4.1.1	The short-term diagnostic model demonstrates that provided the NHS is willing to spend approximately £5000 per additional responder, SeHCAT can be considered cost-effective approximately 50% of the time. We believe this figure could be improved with additional consideration of the following points: For patients in the IBS-D arm (no SeHCAT) the response rate assumed for IBS-D treatment is overly optimistic For those patients in the IBS-D arm (no SeHCAT) who do not respond to treatment there is a good chance there will be additional visits to the GE plus consideration of referral for repeat testing even within the short-term analysis to ensure something has not been missed. This will increase the cost associated with this arm. The model assumes reduced compliance with BAS however it does not take into consideration	Various of the issues brought up here have been responded to in other comments. We leave the judgement whether or not the base case results should be seen as an underestimate to the committee.

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				coleveselam and dietary options which will improve compliance. For patients receiving BAS we believe the daily cost associated with this treatment is an over-estimate plus. In addition, some patients with a diagnosis of BAM will not receive BAS and will be successfully managed with dietary modifications which will likely further reduce the treatment costs associated with the diagnosis of BAM. Given the potential impact on QoL, which is not measured in the short-term model, the probability of cost-effectiveness could be considered an under-estimate.	
4	66.	109	5.4.1.2	While we understand the need for exploration of the different possible scenarios for the long-term analysis we feel that the scenarios presented are generally overly conservative and do not represent a reasonable reflection of what might happen (see comment 72 for additional considerations).	We would welcome the input from expert members of the committee on which long term scenarios are more likely than others.
4	67.	116	5.4.2.1	We strongly question the relevance of this analysis using ToT as a comparator. This is not routine practice in the NHS.	This is for the committee to decide.
4	68.	126	5.4.3.1	The short-term diagnostic model for Crohn's patients	Since there is almost a 1 on 1 relationship

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				demonstrates that provided the NHS is willing to spend approximately £7000 per additional responder, SeHCAT can be considered cost-effective approximately 50% of the time. Given the potential impact on QoL, which is not measured in the short-term model, the probability of cost-effectiveness could be considered an under-estimate (see possible reasons in comment 65).	between % responders and QALYs (only in ToT is this slightly more complicated) there is no reason to assume that the probability of cost-effectiveness would be underestimated.
4	69.	128	5.4.3.1	The short-term diagnostic model for Crohn's patients again demonstrates that provided the NHS is willing to spend up to £5000 per additional responder, SeHCAT can be considered cost-effective. In Figure 3.3 the probability of SeHCAT 10% reaches approximately 70%. We also feel that this could be an underestimate of the cost-effectiveness as additional tests are likely for those patients who do not respond to initial treatment – such costs are not factored into the model.	See comment 3.
4	70.	129	5.4.3.2	We would refer the Committee to comment 34 and highlight that within the more 'reasonable' scenarios, SeHCAT demonstrates cost-effectiveness. Also taking into consideration some of the points raised previous (over-estimate of the cost of BAS; under-estimate of the cost of unresponsive IBS-D patients, etc) we feel that further scenario analyses are	See our response to comment 72 (which is the comment that is referred to by the commentator) and our responses to various similar comments.

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				required to support discussions.	
2	71.	142	5.5	As above – comment 54	We think comment 44 is meant, see our response there.
4	72.	142	5.5	While we understand the need for the various scenario analyses that were performed by the assessment group we would like to highlight to the Committee that some of the scenarios presented are more reasonable than others and should be given more consideration in discussions: Scenarios 1, 2, 8 and 9: assumes that the transition rate from D to ND, and vice versa for both IBS-D and BAM patients are the same (either 0 or 0.05). This is too simplistic Scenario 3 and 10: we would argue that it is more logical and conservative to assume that patients starting the Markov model with diarrhoea remain in this state (0% transition to ND) while a small percentage who start in ND, will transition to D given that patients will stop their treatments and symptoms may recur. SeHCAT is cost-effective in these scenarios, however we do recognise that the probability of cost-effectiveness is only approximately 30%. We would suggest that the results would be	The reason to present all the scenarios was to allow the committee to see if some scenarios might be more likely than others.

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				improved if the cost of IBS-D non-responders was fully reflective of possible additional tests (see comment 4). Scenario 4 and 11: assume too simplistic as there is no transition from ND to D for BAM patients. Scenarios 5 and 12: unrealistic to assume there may be spontaneous remission in the IBS-D arm with no other transitions While the assessment group flag up that when looking at the CEAC for small thresholds the No SeHCAT (treat IBS-D) has the highest probability of being cost-effective, SeHCAT in what we consider to be the more realistic of the scenarios presented does fall within the acceptable CE thresholds. While the CEAC is perhaps low in the current model we would suggest that the probability of cost-effectiveness would increase with the inclusion of a more realistic cost of treating IBS-D patients in the longer term	
4	73.	144	5.5	We agree with the assessment group that there is uncertainty as demonstrated by the various scenarios, however working with the expert members of the Committee we feel that it will be possible to identify more likely scenarios given their practical experience. This will demonstrate the potential value of SeHCAT for the diagnosis of BAM and subsequent appropriate	We would welcome the input from expert members of the committee.

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				treatment.	
2	74.	145	6.1.1	This section repeats many of the errors identified above.	See previous responses.
4	75.	145	6.1.1	We believe the clinical potential of SeHCAT is clear from the available evidence – there is good sensitivity and specificity and an ability to predict the response of patients to BAS given the resulting SeHCAT %. Compared to on-going IBS-D treatment in the absence of SeHCAT this appears a valuable addition to the diagnostic tools available.	See previous responses.
2	76.	146	6.1.1	This summarises the reviewers' error in ignoring many fundamental studies for rather dubious reasons. The reference to Table 57 seems wrong.	This should have been ‘Table 71’.
2	77.	146	Table 71.	Many of these are review articles citing the same references. This table seems no to be cited in the adjacent text.	See previous response.
4	78.	146	6.1.2	We again emphasise that the analysis of ToT as a comparator within this report should not be relevant to the discussion at hand as it is not routine standard practice within the NHS.	This is for the committee to decide.

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2	79.	147	6.1.2	This repeats much data previously given, again with emphasis on the unstudied Trial of treatment,	See previous responses.
4	80.	147	6.1.2	The assessment group did not define a base case in the life time perspective analysis however we feel that it is feasible to identify more realistic scenarios to support the decision making process as noted in comment 72.	See response to comment 72.
4	81.	148	6.1.2	While there is decision uncertainty within the analysis conducted by the assessment group we believe that inclusion of the full potential costs associated with an IBS-D diagnosis (repeat testing and GE visits) and recommendations from experts on the most likely scenarios and their experience will allow the Committee to see the potential benefits associated with SeHCAT in providing patients with a proper diagnosis and allowing the clinician sufficient information to better guide their treatment decisions.	No response required.
4	82.	149	6.2.1	It is a significant strength of SeHCAT that it is long established however it's use has not been extensive due to the lack of recognition of BAM until very recently. The growing recognition of BAM within the IBS-D and Crohn's populations makes this evaluation critical as it will facilitate an even wider recognition that there is an appropriate treatment for these	No response required.

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				patients once they have a confirmed diagnosis.	
2	83.	149	6.2.1	In the numerous reports of several 1000 patients, and adverse events are expected to have been detected.	We do not understand this comment. Is there text missing?
2	84.	150	6.2.1	Surely "test accuracy studies" should use faecal bile acids as the gold standard? See comment 37.	Measurement of faecal bile acids as the gold standard would be one way to improve the available evidence. However, no such studies exist, probably because it is not easy to perform such a study including sufficient patients. Therefore, we have listed other suggestions under research priorities (paragraph 7.2).
4	85.	151	6.2.2	The assessment group have highlighted the considerable differences between studies etc. This is a factor that has been recognised previously as an issue. The BSG state that their recommendations are supported by clinical experience rather than RCTs because of the difficulty in designing appropriate studies in this area (see Guidelines for IBS). We know that the Committee listen carefully to the expert members already but would like to re-emphasise the importance of the expert experience in this evaluation especially around the longer-term outcomes for which	No response required.

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				there is no/limited data to inform the cost-effectiveness model.	
4	86.	152	6.2.2	The assessment group assume within the model that patients not responding to IBS-D treatment will only use loperamide for some symptomatic relief. They recognised that this is a limitation as it is likely some patients will be referred for diagnostic testing to check for organic causes of chronic diarrhoea. It was suggested that at the scoping meeting SeHCAT would not make subsequent testing redundant and therefore the costs would be the same in all strategies. We would ask the Committee to carefully reconsider this assumption as we believe the use of SeHCAT for a diagnosis of BAM can avoid future unnecessary testing. This issue of avoidance of tests was not queried in the survey the assessment group provided to additional experts, which we believe was an important oversight.	At the scoping workshop none of the clinical experts ruled out subsequent testing after a positive SeHCAT test. Therefore, this question was not included in the questionnaire. See also e,g, comment 3.
2	87.	153	6.2.2	Writing as an expert present at the scoping meeting, this was not what was meant. Distinction needs to be made between the short-term and long term investigations in different patients with differing severity of symptoms. The probabilities of different further or repeated investigations varies considerably	This was not how we interpreted the response we got at the scoping workshop. It would be very helpful if these meetings could be minuted to avoid situations like these. Additionally, also see comment 3.

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				when a definite diagnosis is made.	
2	88.	153	6.3.1	Again this paper which did not use SeHCAT is wrongly cited. Only 4/24 D-IBS had BAM (diagnosed by C4)	We agree this study was not in patients with BAM, but in patients with chronic diarrhoea with unknown cause. However, it is the only RCT we could find assessing a BAS.
4	89.	153	6.3.1	It is noted that there is not an appropriate reference standard for this assessment and we would argue that this is because SeHCAT is the first easily available diagnostic test for BAM. While the test itself has been available for many years there has been a lack of recognition of BAM as a possible explanation for persistent chronic diarrhoea. BAM is often far down the list of causes if it is considered at all. While not a life threatening condition, BAM can have a significant impact on a patient's lifestyle. Some undiagnosed patients will have a long history of diarrhoea, sometimes exceeding 10 years. Their bowel-movements can dictate their day-to-day life, limiting travel, their ability to live their home etc.	No response required.

SeHCAT (tauroselcholic [75 selenium] acid) for the investigation of diarrhoea due to bile acid malabsorption

Diagnostics Assessment Report (DAR) - Comments

Responder reference no.	Comment no.	Page no.	Section no.	Comment	EAG Response
4	90.	153	6.3.2	The main uncertainties in the cost-effectiveness are derived from the lack of data on the long-term effectiveness of BAS and the subsequent transition probabilities associated with the treatment of BAM. We would highlighted that the available evidence does demonstrates the value of SeHCAT for the diagnosis of BAM and how it can also support a prediction of the initial response to treatment with BAS. In addition, there is evidence suggestive of a good response to various BAS available (not just considering cholestyramine) plus it is suggested that for some BAM patients dietary modification alone can be sufficient. The potential benefit of an early and accurate diagnosis of BAM must be carefully considered especially in the light of experiences of the experts as a key source of guidance.	We disagree. As described in our report, there is a lack of evidence regarding the diagnostic accuracy of SeHCAT to detect BAM, as well as lack of evidence regarding the effectiveness of treatments for BAM (BAS and diets).
2	91.	156	7.1	This conclusion is not justified by the evidence and ignores much of the data presented or wrongly discarded. The accuracy is very good (but many of the faecal bile acid studies are omitted) and bile acid sequestrants are highly effective for BAM, in these studies and in early studies in groups outside the present scope. Clearly, the economic data, as presented are uncertain, but have not analysed the correct scenario.	See previous responses. No specific studies meeting the inclusion criteria for this review have been mentioned in the previous comments.

SeHCAT (tauroselcholic [75 selenium] acid) for the investigation of diarrhoea due to bile acid malabsorption

Diagnostics Assessment Report (DAR) - Comments

Responder reference no.	Comment no.	Page no.	Section no.	Comment	EAG Response
4	92.	156	7.2	We would argue that the accuracy of SeHCAT test in predicting either BAM or response to treatment is not uncertain. The assessment group themselves note on page 16 that the 3 studies used to assess predicting of treatment were reasonably reliable.	As stated in our report, these studies had small numbers of patients, they used different cut-offs for the assessment of BAM and between study heterogeneity was considerable.