NICE National Institute for Health and Care Excellence

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
GE Healthcare	1.	83	4.2	The discussion acknowledges that the results would appear to indicate that the use of SeHCAT, with a 15% threshold, could identify patients with IBS-D who may benefit from treatment with BAS. We would like to highlight this finding since per indication, SeHCAT is a diagnostic tool. The most recent systematic analysis from [Lyutakov et al. 2019] highlighted that currently SeHCAT continues to have the highest diagnostic yield showing, from all the studies included in their analysis, an average reported sensitivity and specificity of 87.32% and 93.2%, followed by serum C4 with 85.2% and 71.1%, respectively. The diagnostic accuracy of total fecal BA in 48h reached an average sensitivity and specificity of 66.6% and 79.3%, respectively. Fasting serum FGF19 demonstrated the lowest diagnostic yield (63.75% and 72.25% of sensitivity and specificity).	Please see response to comment 2.
GE Healthcare	2.	148	5	The discussion acknowledges that the results would appear to indicate that the use of SeHCAT, with a 15% threshold, could identify patients with IBS-D who may benefit from treatment with BAS. We would like to highlight this finding since per indication, SeHCAT is a diagnostic tool. The most recent systematic analysis from [Lyutakov et al. 2019] highlighted that currently SeHCAT continues to have the highest diagnostic yield showing, from all the studies included in their analysis, an average reported sensitivity and specificity of 87.32% and 93.2%, followed by serum C4 with 85.2% and 71.1%, respectively. The diagnostic accuracy of total fecal BA in 48h reached an average sensitivity and specificity of 66.6% and 79.3%, respectively. Fasting serum FGF19	This statement should not be read as a definitive finding. The discussion also emphasises the wide confidence intervals around the sensitivity estimate from this study and further notes that no patient with a SeHCAT retention value above 15% received a trial of treatment with colestyramine, 'it therefore remains uncertain whether any of these patients could have benefited from treatment with BAS'. Our systematic review identified the review by Lyutakov et al. We consider that this review was generally poorly reported. Although the review makes extensive reference to measures of

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				demonstrated the lowest diagnostic yield (63.75% and 72.25% of sensitivity and specificity).	diagnostic performance (sensitivity and specificity), no inclusion criteria were specified with respect to the reference standard and it was unclear how diagnosis had been determined (reference standard) in individual included studies. There was no indication of how the reported 'average sensitivity and specificity' of SeHCAT had been derived or which studies had informed these estimations. The text of the article states that 8 studies measured SeHCAT retention; all of the 8 studies in the results table that mentioned SEHCAT were identified by our systematic review, of these 4 were evaluations of other tests that used SeHCAT as the reference standard, two were conducted in populations not covered by the scope of this assessment and the remaining two are included in our report (refs. 39 and 43). Overall, we do not consider that the estimates of 'average sensitivity and specificity' of SeHCAT, reported in Lyutakov et can be considered reliable and the review does not add any information to that provided in our report.
GE Healthcare	3.	83	4,2	The evidence that is available with regards to treatment response assessment is an additional value of the diagnostic test. As such, it must be noted that the treatment options vary for the condition and there are several other treatment options being considered aside from the drugs that are currently included in the report. The testing of response of these options as well can be assessed using SeHCAT. Empiric treatment of BAM	We do not consider that evidence linking the results of a diagnostic test to treatment decisions and clinical outcomes is an 'additional value' of a diagnostic test; such evidence is fundamental to establishing the clinical utility of a test. In addition, in cases such as SeHCAT testing for the diagnosis of BAM/BAD, where there is no established reference standard, the use of

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				without a diagnostic justification or driver is highly unlikely to prove effective. Patients who had a positive diagnosis made of BAM/BAD benefitted in terms of symptom improvement. [Fernandes et al. 2019]	treatment response as a reference standard is, in effect, the only viable method of assessing the accuracy of the test. With respect to the variation in treatment options, we acknowledge this as a limitation of our assessment and it is mentioned in our report. Diarrhoea treatment for IBS-D and Crohn's patients may vary greatly between patients, which makes it very difficult to choose a "standard treatment" for the cohort of patients modelled. As in all modelling studies, assumptions had to be made and it was deemed appropriate to base these on experts' input.
GE Healthcare	4.	83	4,2	Merrick et al. reported that more than 15% of the administered selenium radioactivity was retained in the 63 normal subjects (mean age 52 (24-72) years) after one week (median retention 31%, range 16-92%) in their prospective study [Merrick et al. 1985]. The second group consisted of 26 patients who had previously undergone small bowel resection, the third of 29 patients with persistent diarrhoea after previous vagotomy or surgery for peptic ulcer, and the fourth of 51 patients with chronic diarrhoea of non-inflammatory origin--namely, the irritable bowel syndrome in 43, coeliac disease in two, small bowel ischaemia in two, and other miscellaneous conditions in four. None of the 31 patients with irritable bowel disease who retained more than 15% at seven days showed any evidence of small bowel disease, and	We are unclear as to what point is being made by this comment. The content of the comment does not appear to relate to the page and section numbers referenced. A description of the relevant results of the Merrick study is provided in our report, page 57, section 3.2.3 and in Table 4 and Figure 2; the comment provides some additional detail. We are aware of the BSG guidelines and they are cited in our report.

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				none appeared during a follow up of at least 12, and in some up to 24 months. Thirty seven patients retained less than 8% at one week; 23 of these had undergone resection of the ileum, identified in 17 as varying in length from 20 cm to "the entire ileum". Six of the 29 patients who had undergone vagotomy or surgery for peptic ulcer retained less than 8% SeHCAT, as well as 8 other patients with various causes of BAM. Using a lower limit of 15% retention gave a specificity of 0.99 and an upper limit of 8% was associated with a sensitivity of 0.97 to assess BAM, giving an accuracy of 0.88 in the population studied of 106 patients with suspected BAM. The BSG guidelines 2018 recommends that, in people with functional bowel disease or IBS-D, a positive diagnosis of BAM should be made by either SeHCAT testing or serum bile acid precursor C4 (depending on local availability). It states that a SeHCAT retention of 10–15% at 7 days is usually defined as mild bile acid loss, 5–10% as moderate and 0–5% as severely abnormal. The guideline also notes that these values predict response to therapy with bile acid sequestrants, with very low SeHCAT values most likely to respond to treatment.	
UK Bile Acid Related Diarrhoea Network (UK BARDN)	5.	26 / 28 / 29 and others	Background and definition	This is generally a sufficient overview of the problem. We find it surprising that the published survey of UK expert opinion and practice in the diagnosis and management of bile acid diarrhoea (Frontline Gastroenterol 2019;11:358-363) has not been referenced or consulted. However, the opinions of the expert committee members are aligned to the views of this larger body of expert opinion.	We acknowledge the oversight in not including the article on the UK survey of expert opinion and practice, by Walters et al., in the background section of our report. This article was identified by our searches, but did not meet the inclusion criteria for our review. Whilst we endeavour to include as much relevant information as possible in our background

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					sections of our reports, the selection of studies for citation in the background is not a systematic process and hence readers may sometimes find that studies that they are aware of have not been cited.
UK Bile Acid Related Diarrhoea Network (UK BARDN)	6.	27	Care pathway	The BSG Guidelines on Chronic Diarrhoea (2018) are appropriately cited (ref 20) and indicate the benefits to patients of making a positive diagnosis of BAD. The report omits the recently published BSG Guidelines on IBS (Gut 2021; doi:10.1136/gutjnl-2021-324598). These are very relevant and include the recommendation to consider exclusion of BAD with SeHCAT, when it is available.	We acknowledge that the recently published BSG Guidelines on IBS are not cited in our report. These guidelines were first published on 6th April 2021, after the date of the final searches conducted for this assessment.
UK Bile Acid Related Diarrhoea Network (UK BARDN)	7.	33-34	Study design and elsewhere	Bile acid diarrhoea is not defined by a therapeutic response to bile acid sequestrants. There is poor tolerance to sequestrants which are often used sub-optimally, and this should not be a confounding factor in the current assessment the diagnostic value of SeHCAT. There are many studies, particularly after ileal resection (not part of the scope here, but relevant in understanding the role of SeHCAT), that have measured other markers, including total or primary faecal bile acids, or bile acid synthesis (7a-OH-cholesten-3-one). These tests are not clinically widely available in the UK. The data correlating these less convenient tests to SeHCAT are available from earlier observational or cohort studies. It should also be noted that trials of investigational therapeutic agents other than bile acid sequestrants for the treatment of BAD have been performed, and SeHCAT	We acknowledge that therapeutic agents, other than BAS, have been investigated for the treatment of BAD and that, in the article cited, the 10 patients with primary BAD were included on the basis of SeHCAT retention values ≤10%. However, studies which evaluate SeHCAT in the context of treatments other than BAS are outside the published scope and protocol for this assessment.

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				has been found to be effective in predicting the response (e.g. Aliment Pharmacol Ther 2015; 41: 54–64)	
UK Bile Acid Related Diarrhoea Network (UK BARDN)	8.	57-77	3.2.3	In general, this analysis is very thorough, using assessment criteria optimised in the last 10-20 years. Importantly, it recognises the relevance of the earlier, smaller studies from the 1980s when reporting standards were different, such as those by Sciaretta and Merrick (refs 43, 42, 38), which established the current use of SeHCAT. The report makes a balanced assessment of these heterogenous studies with their strengths and limitations. Fig. 2 is convincing.	No response required.
UK Bile Acid Related Diarrhoea Network (UK BARDN)	9.	General		There is little consideration of the impact on patients of a positive diagnosis by SeHCAT test, which has often been delayed because of uncertainties. The findings of the patient group survey (ref 9), and the views of patient representatives are important.	We also acknowledge the importance of the views and experiences of patients. Unfortunately, given the available evidence, it was deemed unfeasible to include any reliable estimates of the effect of delayed diagnosis on the cost effectiveness analyses.
UK Bile Acid Related Diarrhoea Network (UK BARDN)	10.	35 / 242	Excluded studies. Appendix 4	Some of the exclusions of relevant, large studies seem strange. For instance, the senior author on Orekoya et al 2015 (ref 102) is on the committee and could easily provide any additional data requested.	The senior authors on this publication contacted the author who had held the data files and who had moved on from their organisation. Unfortunately this author was no longer able to access the device on which these files had been held.

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Economic Model - Comments

Stakeholder	Comment	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
UK Bile Acid Related Diarrhoea Network (UK BARDN)	1	Use of clinical expert opinion	Clinical expert opinion for many of these questions had been published (Frontline Gastroenterology 2019; see above). This involved estimates of treatment success as judged by 21 members of UK-BARDN	The opinions used are broadly in alignment with those from the larger group.	Please see collated DAR comments, response to comment 5.
UK Bile Acid Related Diarrhoea Network (UK BARDN)	2	The economic benefits of making a positive diagnosis of BAD will be greater if the analysis had included costs of other investigations for chronic diarrhoea (ref 2).	There are multiple other causes of chronic diarrhoea. Microscopic colitis, occurring in 10%, has explicitly been excluded from the analysis. Investigations for neuroendocrine tumours, exocrine pancreatic insufficiency, small intestinal bacterial overgrowth, motility disorders, and pelvic floor dysfunction have not been factored in and may be needed in the absence of a sensitive and specific test to make the diagnosis of BAD.	Inclusion of these tests in the model will increase the costs in the arms not investigated by SeHCAT. The benefit from use of SeHCAT will be greater.	We acknowledge this as a limitation of our study. Our population of interest is as described here: 'This chapter explores the cost effectiveness of including SeHCAT testing in the diagnostic pathway for investigation of diarrhoea due to BAM in adults with IBS-D or FD and in adults with Crohn's disease without ileal resection.' i.e. does not explicitly include other causes, but we did not want to rule out the possibility of having missed some other causes and so, despite there being almost no evidence of how many cases there might be, we included IBD in the modelling. However, we would like to note that including in the model all these other causes of chronic diarrhoea would require an enormous amount

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					of data for which we believe there is currently no evidence. We agree that including these tests would increase the costs in the arms not investigated by SeHCAT but it may also increase the response rate associated to these investigations. Therefore, it is uncertain whether and to what extent, the benefit from use of SeHCAT will be greater.