NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Diagnostics consultation document

SeHCAT (tauroselcholic [75 selenium] acid) for diagnosing bile acid diarrhoea

The National Institute for Health and Care Excellence (NICE) is producing guidance on using SeHCAT in the NHS in England. The diagnostics advisory committee has considered the evidence and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence (the diagnostics assessment report).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the recommendations may need changing to meet these aims. In particular, please tell us if the recommendations:

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- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have about such effects and how they could be avoided or reduced.

Note that this document is not NICE's final guidance on SeHCAT. The recommendations in section 1 may change after consultation.

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering the comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the diagnostics assessment programme manual.

Key dates:

Closing date for comments: 4 August 2021

Second diagnostics advisory committee meeting: 19 August 2021

1 Recommendations

1.1 There is not enough evidence to recommend routine use of SeHCAT (tauroselcholic [75 selenium] acid) for diagnosing bile acid diarrhoea in people with:

- chronic diarrhoea with an unknown cause, suspected or diagnosed diarrhoea-predominant irritable bowel syndrome (IBS-D) or functional diarrhoea
- Crohn's disease without ileal resection who have chronic diarrhoea.

1.2 Further research is recommended (see section 5) on:

- how SeHCAT test results affect decisions about treatment and clinical outcomes
- the tolerability and effectiveness of treatments for bile acid diarrhoea
- the health-related quality of life of people with bile acid diarrhoea.

1.3 Centres currently using SeHCAT for diagnosing bile acid diarrhoea should do so as part of research or further data collection (see section 5).

Why the committee made these recommendations

SeHCAT is a radiopharmaceutical test for diagnosing bile acid diarrhoea. It was recommended for use only in research in 2012 because of limited clinical evidence.

Although there is now some more clinical evidence, it remains limited in quantity and quality. Most studies are small and give results only for people who had a positive SeHCAT test result. It is unclear how the test results are used to guide management of bile acid diarrhoea, and how well people

tolerate treatment. So it is uncertain how having a diagnosis affects longer-term clinical outcomes.

The limited clinical data means that the economic model includes many assumptions. The results are highly uncertain and SeHCAT's cost effectiveness cannot be determined. So, although SeHCAT shows promise, further research is needed.

2 The diagnostic tests

Clinical need and practice

2.1 In bile acid diarrhoea, a form of chronic diarrhoea, the body does not recycle bile acids properly. It is most commonly caused when bile acids are overproduced in people who have no damage to the bile acid recycling system. Bile acid diarrhoea can also be a secondary condition, if the small bowel or another part of the bile acid recycling system is damaged, for example by disease or surgery.

2.2 Symptoms of bile acid diarrhoea are usually managed with bile acid sequestrant medication. Three products are available: colestyramine, colestipol and colesevelam.

The intervention

SeHCAT

2.3 SeHCAT (tauroselcholic [75 selenium] acid) is a diagnostic radiopharmaceutical capsule used to measure how well the body absorbs bile acids. It contains 75 selenium (a gamma emitter) and a synthetic bile acid (tauroselcholic acid). When swallowed, the body absorbs SeHCAT like a natural bile acid. It can be detected in the body by a scan using a gamma camera.

2.4 A SeHCAT test involves 2 outpatient appointments in a hospital's nuclear medicine department. At the first appointment (day 1), the person swallows a SeHCAT capsule, waits for up to 3 hours and has a baseline scan. At the second appointment (day 7), they have a follow-up scan. People may need to stop anti-diarrhoeal medication for the duration of the test because it may affect the result.

2.5 The test result shows how much SeHCAT remains in the body. To calculate this, the amount of radioactivity detected in the follow-up scan is divided by the amount of radioactivity detected in the baseline scan. Bile acid diarrhoea is usually diagnosed when around 15% or less SeHCAT remains in the body.

The comparators

2.6 The comparators are:

- no SeHCAT testing and no bile acid sequestrants
- no SeHCAT testing and a trial of bile acid sequestrants.

3 Evidence

The diagnostics advisory committee considered evidence on SeHCAT for investigating bile acid diarrhoea from several sources. Full details of all the evidence are in the project documents on the NICE website.

3.1 The clinical and cost effectiveness of SeHCAT for investigating bile acid diarrhoea was assessed in people with:

- chronic diarrhoea with an unknown cause, suspected or diagnosed diarrhoea-predominant irritable bowel syndrome (IBS-D) or functional diarrhoea (primary bile acid diarrhoea)
- Crohn's disease without ileal resection who have chronic diarrhoea (secondary bile acid diarrhoea).

Clinical effectiveness

3.2 A systematic review of clinical effectiveness evidence by the external assessment group (EAG) identified 24 observational studies relevant to this assessment. No randomised controlled trials were identified. Of the 24 studies, 21 described outcomes only for some of the people who had a positive SeHCAT test result. The remaining 3 studies assessed how well the SeHCAT test predicts response to bile acid treatment (predictive accuracy). Heterogeneity between the studies was high and the quality of the studies was considered low.

Predictive accuracy of SeHCAT in suspected or diagnosed IBS-D or functional diarrhoea

3.3 The 3 small studies evaluating the predictive accuracy of SeHCAT were included in the previous assessment. They assessed the relationship between the SeHCAT test result and response to colestyramine treatment. Table 1 summarises the predictive accuracy estimates for the different SeHCAT thresholds that the studies reported. Because of the small number of studies, and differences in study characteristics and test thresholds, a pooled estimate of predictive accuracy was not calculated.

Table 1 Accuracy of SeHCAT for predicting response to bile acid sequestrants in suspected or diagnosed IBS-D or functional diarrhoea

Study	Study size	Threshold	Sensitivity	95% confidence interval (CI)	Specificity	95% CI
Merrick et al. (1985)	43	<8%	0.667	0.223 to 0.957	0.971	0.847 to 0.999
Merrick et al. (1985)	43	≤15%	1.000	0.541 to 1.000	0.912	0.763 to 0.981
Sciaretta et al. (1986)	13	<5%	0.857	0.421 to 0.996	1.000	0.541 to 1.000
Sciaretta et al. (1987)	46	<8%	0.950	0.751 to 0.999	0.962	0.804 to 0.999

Response to bile acid sequestrants after a positive SeHCAT test in suspected or diagnosed IBS-D or functional diarrhoea

3.4 In total, 8 studies evaluated the probability of response to bile acid sequestrants after a positive SeHCAT test at a 15% threshold. Only 2 of these were new studies found through the searches in this assessment. The median response rate in these 8 studies was 68% (range 38% to 86%). Between 70% and 100% of people had bile acid sequestrant treatment after a positive SeHCAT test. Because of the substantial differences between studies, meta-analysis of the response rate was considered inappropriate.

Effects of treatment on bowel symptoms in suspected or diagnosed IBS-D or functional diarrhoea

3.5 In addition to reporting the probability of response to treatment after a positive SeHCAT test, 3 of the studies described the effects of bile acid sequestrants on bowel symptoms. In these studies, colestyramine was described as improving stool consistency, reducing daily bowel movements and stool frequency, and removing the urgency of needing the toilet.

Tolerability of bile acid sequestrants in suspected or diagnosed IBS-D or functional diarrhoea

3.6 There were 8 studies reporting the proportion of people who found bile acid sequestrants difficult to tolerate or stopped their treatment for unclear reasons. Rates of intolerance and discontinuation were generally high (median 15%, range 4% to 27%). There was not enough information to determine whether these rates varied between the different types of bile acid sequestrants.

Health-related quality of life of people with suspected or diagnosed IBS-D or functional diarrhoea

3.7 There were 2 studies reporting changes in health-related quality of life in people who had bile acid sequestrants after a positive SeHCAT test result. One study evaluated quality of life using the SF-36 questionnaire after 8 weeks of cholestyramine. There were improvements in the general pain domain in people with mild bile acid diarrhoea (defined as a positive SeHCAT test result at a threshold between 11% and 15%, $p<0.05$). There were also improvements across many other domains (emotional problems, energy or fatigue, emotional wellbeing, social functioning, general health, health change) in people with more severe bile acid diarrhoea (threshold 5% or less, $p<0.05$). Another study reported improvements in activity levels sub score ($p=0.00998$) using the EQ-5D questionnaire in people who had colestyramine or colesevelam. This study did not report either the threshold used to define a positive SeHCAT test result or the duration of follow up.

Evidence in Crohn's disease

3.8 No evidence was found for the predictive accuracy of SeHCAT or for patient-reported outcomes in people with Crohn's disease without ileal resection who have chronic diarrhoea.

3.9 Only 1 small study (Smith et al. 2000) evaluated the probability of response to bile acid sequestrants (colestyramine or colestipol) after a positive SeHCAT test in 44 people with Crohn's disease. This study was included in the previous assessment. The threshold used to define a positive SeHCAT test was 10%. In this study, 24 (55%) people had a positive SeHCAT test result at a 10% threshold. But only 9 of these 24 (38%) people had bile acid sequestrants. This treatment was considered to work for 8 of these 9 people (89%).

Cost effectiveness

Economic model

3.10 The EAG developed 2 de novo economic models to assess SeHCAT's cost effectiveness for investigating and diagnosing bile acid diarrhoea in the populations in the scope of this assessment. The models used a lifetime (50 years) time horizon to estimate outcomes in terms of quality-adjusted life years (QALYs) and costs from an NHS perspective.

3.11 The models included:

- a short-term decision analytic model that captured the diagnostic pathway and initial response to treatment (first 6 months)
- a long-term Markov model that estimated the lifetime costs and effects for people having treatment.

3.12 SeHCAT testing, using a 15% threshold value for a positive test, was compared with these strategies:

- no SeHCAT testing and no bile acid sequestrants
- no SeHCAT testing and a trial of bile acid sequestrants.

Model inputs for suspected or diagnosed IBS-D or functional diarrhoea

3.13 When possible, model inputs were based on the clinical effectiveness systematic review or other published literature. When such evidence was not available, expert opinion was used. This was obtained from a questionnaire the EAG sent to the clinical expert specialist committee members for this assessment.

3.14 The probability of a positive SeHCAT test result in the base case was a pooled estimate of 45.4%, calculated from the 8 studies in the systematic review that used SeHCAT at a 15% threshold.

3.15 People who were offered bile acid sequestrants had either colestyramine or colesevelam. Based on the responses to EAG's questionnaire, it was assumed that 50% of people in the SeHCAT strategy and 85% of people in the trial of treatment strategy started colestyramine.

3.16 The probability of response to bile acid sequestrants after a positive SeHCAT test result was a pooled estimate of 63.8%, from the 8 studies using SeHCAT at a 15% threshold. In the trial of treatment strategy, based on expert opinion, the treatment response was estimated as 30%. Based on the available evidence, it was not possible to distinguish between the response to colestyramine and colesevelam.

3.17 Expert opinion suggested that colestyramine may be difficult to tolerate so people may be offered colesevelam instead. In both the SeHCAT strategy and the trial of treatment strategy, the probability of switching from colestyramine to colesevelam was estimated to be 50% based on expert opinion.

3.18 The probability of having a colonoscopy in the model was estimated based on expert opinion:

- For people who had a negative SeHCAT test result or when bile acid sequestrant treatment after a positive SeHCAT test did not work, the probability was 49%.
- For people who had not had a SeHCAT test or a trial of bile acid sequestrants, the probability was 74%.
- For people who had a trial of treatment that had not worked, the probability was 90%.

3.19 The probability of being diagnosed with inflammatory bowel disease (IBD) after the colonoscopy was likely to be very low. This was supported by expert opinion, and a study (Patel et al. 2015) that reported the number of people with IBS-D-like symptoms who were eventually diagnosed with IBD. Based on this, the proportion of people who would be diagnosed with IBD after colonoscopy was estimated to be 5.3%. Based on expert opinion, the probability of response to IBD treatment was estimated to be 72%.

3.20 The estimated probabilities of having a colonoscopy and a diagnosis of IBD (5.3% of the people having a colonoscopy) meant that most people, about 96%, would be offered IBS-D treatment. The probability of IBS-D treatment response, after a colonoscopy that ruled out IBD, was estimated based on expert opinion:

- For people who had a negative SeHCAT test result, the probability was 56%.
- For people who had not had a SeHCAT test or a trial of bile acid sequestrants, the probability was 46%.
- For people whose bile acid sequestrant treatment had not worked, the probability was 50%.

Based on these estimates, the EAG calculated that the probability of IBS-D treatment response would be slightly lower for people who had not had a colonoscopy to rule out IBD:

- For people who had a negative SeHCAT test result, the probability was 53%.
- For people who had not had a SeHCAT test or a trial of bile acid sequestrant, the probability was 44%.
- For people whose bile acid sequestrant treatment had not worked, the probability was 47%.

3.21 The long-term Markov model included health states for 'diarrhoea', 'no diarrhoea' and 'death'. Assumptions about people moving between the 'diarrhoea' and 'no diarrhoea' health states were informed by expert opinion. This suggested that, in general, the response to bile acid sequestrants and to IBS-D treatment is expected to last without relapses. So no movement from the 'no diarrhoea' to the 'diarrhoea' health state in the long term should be expected. With IBD treatment, the experts noted that relapses are expected to occur after the initial response to treatment. Therefore, in the long-term Markov model it was assumed that people having IBD treatment would move between the 'diarrhoea' and 'no diarrhoea' health states. Based on expert opinion, the EAG assumed that people having IBD treatment have an average of 1 relapse every 5 years. So, the base-case probability of people having IBD treatment moving from the 'no diarrhoea' to 'diarrhoea' health state was estimated as 0.45%.

3.22 The base case assumed that no excess mortality was associated with bile acid diarrhoea.

Health-related quality of life in suspected or diagnosed IBS-D or functional diarrhoea

3.23 The utility values used were the same as in the previous assessment (see table 2). Because colestyramine can be difficult to tolerate, it was assumed that people for whom colestyramine

worked had a slightly lower (75%) utility gain from their treatment. The model did not include utility loss for colonoscopy.

Table 2 Utility values used in the base case for people with suspected or diagnosed IBS-D or functional diarrhoea

Health state	Subpopulation	Utility value	Source
No diarrhoea	People for whom colesevelam, IBS-D or IBD treatment works (treatment response)	0.776	Pooled estimate from Mearin et al. (2004) and Spiegel et al. (2009)
No diarrhoea	People for whom colestyramine treatment works (treatment response)	0.760	Assumption
Diarrhoea	People for whom bile acid sequestrant, IBS-D or IBD treatment does not work (no treatment response)	0.712	Pooled estimate from Mearin et al. (2004) and Spiegel et al. (2009)

Abbreviations: IBS-D, diarrhoea-predominant irritable bowel syndrome; IBD, inflammatory bowel disease

Costs for suspected or diagnosed IBS-D or functional diarrhoea

3.24 The company's cost for SeHCAT was £195 per capsule. The cost of administering it in the NHS was £282 per test, taken from the NHS national tariff for 2021/22. Therefore, the total cost of a SeHCAT test in the base case was £477 per test.

3.25 Other costs considered in the model included the costs of bile acid sequestrants, IBS-D treatment, IBD treatment and colonoscopy (see table 3).

Table 3 Costs of medications, additional treatments and colonoscopy in the model for people with suspected or diagnosed IBS-D or functional diarrhoea

Resource	Cost per person per day	Sources
Bile acid sequestrants: colestyramine	£0.35	BNF, expert opinion
Bile acid sequestrants: colesevelam	£2.56	BNF, expert opinion
IBS-D treatment: medication	£0.06	BNF, expert opinion
IBS-D treatment: diet therapy	£12.24	NHS national tariff, expert opinion
IBS-D treatment: psychological therapy	£35.74	NHS national tariff, expert opinion
IBD treatment: medication	£21.73	BNF, expert opinion
IBD treatment: diet therapy	£149.00	NHS national tariff, expert opinion
IBD treatment: psychological therapy	£289.33	NHS national tariff, expert opinion
Colonoscopy	£175.75	NHS national tariff, expert opinion (90% conventional colonoscopy and 10% CT colonoscopy)

Abbreviations: IBS-D, diarrhoea-predominant irritable bowel syndrome; IBD, inflammatory bowel disease

Base-case assumptions in suspected or diagnosed IBS-D or functional diarrhoea

3.26 These key assumptions were applied in the base-case analysis:

- People whose condition responds to bile acid sequestrant treatment have bile acid diarrhoea.
- Treatment for bile acid diarrhoea includes only bile acid sequestrants, either colestyramine or colesevelam.
- Some people will switch to colesevelam early in the treatment because colestyramine may be difficult to tolerate.

- People for whom bile acid sequestrant or IBS-D treatment works in the short term will continue and will benefit from it for the rest of their life.
- People who take colesevelam will have better quality of life than people who take colestyramine.
- Some people who have not had a SeHCAT test, or who have a negative SeHCAT test result, or for whom bile acid sequestrants have not worked in the short term, will have a colonoscopy to detect IBD.
- Some people for whom IBD treatment works in the short term will have relapses throughout their life.
- People for whom none of the treatments offered have worked in the short term are assumed to take loperamide for the rest of their life.
- All the resource use estimates are based on expert opinion.

Model inputs for Crohn's disease

3.27 The clinical effectiveness systematic review found only 1 study that reported the probability of a positive SeHCAT test in people with Crohn's disease without ileal resection who have chronic diarrhoea. This probability of 55% was used in the base case.

3.28 People who were offered bile acid sequestrants started either colestyramine or colesevelam. Based on expert opinion, it was assumed that 63% of people in the SeHCAT strategy and 58% of people in the trial of treatment strategy started colestyramine.

3.29 The probability of response to treatment after a positive SeHCAT test result at a 15% threshold was estimated as 89% in the base case. This came from the same small study that provided data for the probability of a positive SeHCAT test result. It was higher than the maximum 70% probability of response estimated by the clinical experts. In the trial of treatment strategy, based on expert opinion,

the treatment response was estimated as 33%. Based on the available evidence, it was not possible to distinguish between the response to colestyramine and colesevelam.

3.30 In both the SeHCAT and the trial of treatment strategies, the probability of switching from colestyramine to colesevelam because of poor tolerability was estimated to be 44% based on expert opinion.

3.31 Treatment options for diarrhoea in Crohn's disease may vary depending on whether they treat diarrhoea because of relapse or prevent diarrhoea during remission. Because of this, it was not possible to find data from the literature showing how well diarrhoea treatment in Crohn's disease might work. Therefore, the probability of Crohn's disease treatment response was estimated based on expert opinion:

- For people who had a negative SeHCAT test result, the probability was 42%.
- For people who had not had a SeHCAT test or a trial of bile acid sequestrants, the probability was 40%.
- For people whose bile acid sequestrant treatment had not worked, the probability was 41%.

3.32 Assumptions about people moving between the 'diarrhoea' and 'no diarrhoea' health states were informed by expert opinion. This suggested that, in general, the response to bile acid sequestrants is expected to last. So, no relapses and no movement from the 'no diarrhoea' to the 'diarrhoea' health state in the long term should be expected. For diarrhoea treatment for Crohn's disease, the experts expected that relapses would occur after the initial response to treatment. Therefore, in the long-term Markov model it was assumed that people having this treatment would move between the 'diarrhoea' and 'no diarrhoea' health states. As with people

having IBD treatment in the IBS-D or functional diarrhoea model, it was assumed that people having diarrhoea treatment for Crohn's disease would have an average of 1 relapse every 5 years. So, the base-case probability of people on this treatment moving from the 'no diarrhoea' to 'diarrhoea' health state was estimated as 0.575%.

3.33 The base case assumed that no excess mortality was associated with bile acid diarrhoea. A pooled standardised mortality ratio estimate from a meta-analysis of mortality in Crohn's disease by Canavan et al. (2007) was applied to the overall UK mortality estimates.

Health-related quality of life in Crohn's disease

3.34 No studies on health-related quality of life in people with Crohn's disease and diarrhoea were found. The estimate from a study providing utilities for people with active Crohn's disease (Buxton et al. 2007) was assumed to also reflect quality of life in the diarrhoea health state. To estimate the utility gain for people for whom the treatment worked, it was assumed that the utility loss because of diarrhoea was the same as for people with IBS-D or functional diarrhoea. As in the IBS-D or functional diarrhoea model, it was assumed that the utility gain from colestyramine would be slightly lower than from the other treatments. Table 4 summarises the utility values used.

Table 4 Utility values used in the base case in people with Crohn's disease

Health state	Subpopulation	Utility value	Source
No diarrhoea	People for whom colesevelam or treatment of diarrhoea in Crohn's disease works (treatment response)	0.764	Assumption
No diarrhoea	People for whom colestyramine treatment works (treatment response)	0.748	Assumption
Diarrhoea	People for whom bile acid sequestrants or treatment of diarrhoea in Crohn's disease does not work (no treatment response)	0.700	Estimate from Buxton et al. (2007)

Costs for Crohn's disease

3.35 The total cost of SeHCAT in the base-case model was £477 per test, the same as in the IBS-D or functional diarrhoea model.

3.36 The costs of treating bile acid diarrhoea with bile acid sequestrants were £0.35 per person per day for colestyramine and £2.56 per person per day for colesevelam. These were the same as in the IBS-D or functional diarrhoea model.

3.37 The cost of the medication for treating diarrhoea in Crohn's disease was £5.76 per person per day. This was estimated using BNF prices, and the average dosages and proportion of people having different types of medication reported by the experts in the previous assessment.

Base-case assumptions in Crohn's disease

3.38 Except for the assumption about colonoscopy, the key assumptions used in the base-case analysis for people with suspected or diagnosed IBS-D or functional diarrhoea were also applied in the

base-case analysis for people with Crohn's disease without ileal resection who have chronic diarrhoea.

3.39 These key assumptions were also applied:

- Everyone has had a colonoscopy to diagnose Crohn's disease.
- People who have not had a SeHCAT test, or who have a negative SeHCAT test result, or whose bile acid sequestrant treatment has not worked in the short term, will be offered treatment for diarrhoea in Crohn's disease.
- Some people with Crohn's disease for whom the diarrhoea treatment works in the short term will have relapses throughout their life.

Base-case results in suspected or diagnosed IBS-D or functional diarrhoea

3.40 The SeHCAT strategy was more effective and less expensive (dominant) than the strategy of offering a trial of bile acid sequestrants. It was also more effective but more expensive than the strategy in which bile acid diarrhoea was not investigated or treated. The incremental cost-effectiveness ratio (ICER) for the SeHCAT strategy compared with this strategy was £9,661 per QALY gained (probabilistic base-case analysis).

3.41 In the short term, the SeHCAT strategy had the lowest rate of colonoscopies and the lowest cost per colonoscopy avoided. It also had the highest rate of treatment response (any type of treatment). The initial costs of the SeHCAT strategy were the highest because of the costs of the SeHCAT test. The results of the deterministic and probabilistic analyses were similar.

Secondary analysis in suspected or diagnosed IBS-D or functional diarrhoea

3.42 In this analysis, it was assumed that colonoscopy was not offered to people:

- who had no SeHCAT test
- who had a negative SeHCAT test result
- whose bile acid sequestrant treatment did not work.

3.43 As with the base-case analysis, the SeHCAT strategy provided the highest QALYs. But in this analysis, it was more expensive than the strategy in which no testing and no bile acid sequestrant was offered and the strategy in which a trial of treatment was offered. The ICER for the SeHCAT strategy compared with the trial of treatment strategy was £21,036 per QALY gained (probabilistic base-case analysis).

3.44 In the short term, as in the base-case scenario, the SeHCAT strategy had the highest rate of treatment response. Initial costs of the SeHCAT strategy were again the highest because of the costs of the SeHCAT test. The results of the deterministic and probabilistic analyses were similar.

Analysis of alternative scenarios in suspected or diagnosed IBS-D or functional diarrhoea

3.45 Robustness of the cost-effectiveness results to alternative model assumptions was considered in several scenario analyses. In nearly all the scenarios, the cost-effectiveness results were similar to the base case or SeHCAT produced ICERs around or below £20,000 per QALY gained. In the scenarios in which another strategy could be considered the most cost-effective option (where the probability of colonoscopy is set to 0, and the probability of

response to IBS-D treatment is lower in the SeHCAT arm), the model assumptions were likely to be unrealistic.

Base-case results in Crohn's disease

3.46 In both the deterministic and probabilistic base-case analyses, the SeHCAT strategy was the most cost effective. In the deterministic analysis, it was more expensive but also more effective than the strategy of offering a trial of a bile acid sequestrant. The ICER for the SeHCAT strategy compared with this strategy was £1,727 per QALY gained (deterministic base-case analysis). In the probabilistic analysis, it was both more effective and less expensive than the trial of treatment strategy. In both analyses, the strategy in which bile acid diarrhoea was not investigated or treated was more expensive and less effective than the other strategies. The total costs of all the strategies in the probabilistic analysis were higher than the total costs in the deterministic analysis. This was because it was assumed in the probabilistic analysis that within the possible cost range, the costs would more often be higher than lower.

3.47 In the short term, the SeHCAT strategy had the highest treatment response rate to any type of medication. But the initial costs were higher than in the trial of treatment strategy because of the costs of the SeHCAT test. Cost per response was the lowest for the trial of treatment strategy.

Analysis of alternative scenarios in Crohn's disease

3.48 Robustness of the cost-effectiveness results to alternative model assumptions and parameters was considered in several scenario analyses. In nearly all the scenarios, the cost-effectiveness results were similar to the base case or SeHCAT-produced ICERs at below £9,500 per QALY gained. In the scenarios in which another strategy could be considered the most cost-effective option, the model assumptions were likely to be unrealistic.

4 Committee discussion

Bile acid diarrhoea is now better recognised as a condition

4.1 The clinical experts explained that since NICE published guidance on SeHCAT in 2012, awareness of bile acid diarrhoea as a condition has increased. They estimated that 1 in 20 people referred to a gastroenterology clinic because of chronic diarrhoea may have bile acid diarrhoea. Testing means that this condition can be identified and distinguished from diarrhoea-predominant irritable bowel syndrome (IBS-D), and treatment offered. Clinicians now agree that it is important to be able to test for bile acid diarrhoea and to treat it.

Having a diagnosis of bile acid diarrhoea is helpful

4.2 The patient experts explained that having bile acid diarrhoea can affect quality of life and limit daily activities such as ability to work. Diagnosing bile acid diarrhoea is important because it explains the person's symptoms and means they can have treatment. Also, it can support a request for reasonable adjustments at work. The committee considered how having a diagnosis affects treatment with bile acid sequestrants. These are unpleasant to take and many people do not adhere to treatment. The clinical experts explained that people who have a diagnosis of bile acid diarrhoea may be more motivated to continue them than people who start them as a trial of treatment. The committee recognised that having a diagnosis of bile acid diarrhoea is helpful.

Clinical effectiveness

Evidence on the effects of SeHCAT testing in Crohn's disease is very limited

4.3 The external assessment group's (EAG) systematic review on the clinical effectiveness of SeHCAT testing (see section 3) found only

1 study in people with Crohn's disease. The committee concluded that SeHCAT testing in this population could be useful but there is not enough data available to understand its benefits and harms. It recommended that further research is done to show the clinical effectiveness of SeHCAT testing in people with Crohn's disease (see sections 5.1 to 5.4).

Evidence on the effects of SeHCAT testing in people with primary bile acid diarrhoea is limited in quality

4.4 There were 9 new studies published since NICE's original guidance in 2012. So, 24 studies in total were available for the primary bile acid diarrhoea population. Most of these provided data on response to treatment after a positive test result. The committee noted that the populations in these studies did not reflect the people who would be seen in NHS clinical practice. This is because people with chronic diarrhoea in the NHS are likely to be offered tests to identify other conditions with similar symptoms first, before SeHCAT testing. The populations in the studies were not likely to have had faecal immunochemical tests and faecal calprotectin tests before SeHCAT because the studies pre-date their introduction. Also, the committee noted that the studies were often small and had methodological limitations. Most only described limited short-term outcomes. It recommended that further research is done to show the clinical effectiveness of SeHCAT testing in people with primary bile acid diarrhoea (see sections 5.1 to 5.4).

It is uncertain how SeHCAT test results affect decisions about treatment

4.5 The committee noted that although most studies described response to treatment after a positive SeHCAT test result, not everyone with a positive test result was offered bile acid sequestrants. Between 70% and 100% of people who had a

positive SeHCAT test at a 15% threshold had bile acid sequestrants. The studies provided no information on how treatment decisions were made and it was unclear whether some people with negative test results would also get treatment. The committee concluded that research was needed to better understand how the test results affect treatment decisions (see section 5.1).

Outcomes for people with negative test results are not clear

4.6 The evidence described outcomes only for people who had a positive SeHCAT test result. The committee recognised that the potential benefits and harms of testing for people who had a negative test result are not clear. The clinical experts explained that in people who do not have bile acid diarrhoea, the synthetic bile acid in the SeHCAT capsule remains in the body for a long time. Although it contains a low level of radiation, the half-life of 75 selenium is almost 4 months. The committee noted that people with a negative test result retain some radiation in their body and it was unclear how these people might benefit from having the test. The committee concluded that although the radiation levels in SeHCAT are low and the test is safe, evidence from people with a negative test result is needed. This is to fully understand the benefits and harms of the SeHCAT test (see section 5.2).

The tolerability and effectiveness of different treatment options for bile acid diarrhoea are not clear

4.7 The committee noted that based on the evidence, it was not possible to estimate the effectiveness of the different bile acid sequestrants for treating bile acid diarrhoea. No evidence was found on the long-term effects of the bile acid sequestrants. It was unclear whether they have a sustained effect on bile acid diarrhoea and if they have any negative effects such as reducing vitamin absorption. The patient experts highlighted how important it is to

better understand the tolerability of different bile acid sequestrants. The committee noted that many studies reported high rates of treatment discontinuation, but it was not clear whether the rates were the same for colestyramine and colesevelam. None of the studies used colestipol. The committee concluded that further research is needed to assess tolerability and effectiveness of the treatment options for bile acid diarrhoea (see section 5.3).

How severity of bile acid diarrhoea affects health-related quality of life is not clear

4.8 The committee noted that there was very limited evidence on the health-related quality of life of people with bile acid diarrhoea and whether treatment would improve this. The patient experts explained that the severity of symptoms and how much bile acid sequestrants improve symptoms may vary. The more severe the symptoms, the more effect treatment is likely to have. However, they explained that treatment is unlikely to completely resolve symptoms. This is because many people have flare-ups despite long-term treatment, especially when they have bile acid diarrhoea and irritable bowel syndrome. The committee noted that severe symptoms are more likely to be associated with reduced quality of life than less severe symptoms, but how much more likely is unknown. Further research on how severity of bile acid diarrhoea affects health-related quality of life and how this may change over time with and without treatment is needed (see section 5.4).

Cost effectiveness

How SeHCAT testing affects clinical outcomes is uncertain

4.9 The committee considered the assumptions used in the economic model. It noted that, because of the lack of clinical outcome data, most of the model inputs were estimated based on expert opinion from a small group of clinicians. The clinical experts explained that

they were not confident that their estimates captured the variability of bile acid diarrhoea seen in practice. The committee was not certain that the analyses presented had fully quantified the uncertainty caused by the lack of clinical outcome data. It concluded that the modelling should be considered exploratory.

Modelling the use of SeHCAT at a 15% threshold for a positive test result is appropriate

4.10 The EAG assumed that a threshold of 15% retention of SeHCAT would be used to define a positive test result in its model. The committee discussed whether this threshold was appropriate. The evidence was too limited to estimate how bile acid sequestrants might benefit people who have a positive test result at different SeHCAT thresholds. But it noted that in most studies a 15% threshold was used to define a positive SeHCAT test result. The clinical experts explained that the threshold used in practice varies. Treatment may also work for people with a positive test at higher thresholds, but 15% was a widely used and accepted threshold. The clinical experts noted that the 15% threshold was also supported by 2 recent surveys of SeHCAT use. The committee concluded that although the evidence did not allow the optimal threshold to be explored, it was reasonable to assume a 15% threshold in the model.

The resource impact of preventing colonoscopies when SeHCAT is used is captured in the analyses

4.11 Since NICE published the original guidance in 2012, the place of SeHCAT in the care pathway has changed. The EAG included the possibility of having a colonoscopy after SeHCAT testing in the model for people with suspected or diagnosed IBS-D or functional diarrhoea. The committee considered whether this reflected current practice and whether using SeHCAT could help reduce the number

of colonoscopies done. The clinical experts explained that most colonoscopies are avoided because blood and stool tests are used to exclude inflammation before a SeHCAT test (see section 4.4). They noted that clinical practice varies but variation in the timing of colonoscopies (before or after SeHCAT testing) was adequately reflected in the modelling. The committee noted that the cost of colonoscopy was included in the model. It concluded that the resource impact of preventing colonoscopies was adequately captured. The committee questioned whether the model should also have included disutility associated with colonoscopy. The EAG explained that the disutility was not included because of a lack of data. But it noted that the model assumes colonoscopy occurs only in the 6 months immediately after a SeHCAT test. So, the committee concluded that it was unlikely that including a disutility for colonoscopy would change the overall conclusions of the cost-effectiveness analyses.

The model is unlikely to capture the full costs of providing SeHCAT testing

4.12 The committee discussed whether all the relevant costs involved in providing SeHCAT testing had been included in the model. The clinical experts explained that because the level of radioactivity in SeHCAT is low, other investigations using radioactivity could interfere with the test results. So, nuclear medicine departments cannot do other investigations when doing SeHCAT testing. The committee concluded that the cost of providing SeHCAT testing was unlikely to be fully captured in the model.

The model does not reflect the variable severity of bile acid diarrhoea

4.13 The long-term Markov model included a health state for people who have diarrhoea (because the treatment did not work) and a health

state for people who do not have diarrhoea (because the treatment worked). The committee recalled its discussion on the severity of bile acid diarrhoea and how this could affect quality of life (see section 4.8). It concluded that the model did not capture the effects of variable diarrhoea severity and treatment response.

The relative value of SeHCAT testing may be overestimated in the model

4.14 The committee discussed whether it was appropriate to assume that response to bile acid sequestrants in the trial of treatment strategy was lower than in the SeHCAT strategy. This assumption was based on expert opinion. It recalled that the clinical experts highlighted that they were not confident of their answers to the questionnaire used to obtain values for the model. Assuming a lower probability of treatment response in the trial of treatment strategy would bias the model results towards SeHCAT and make it appear more cost effective. The committee concluded that using expert opinion without accounting for the discrepancies in treatment response for each of the strategies affected the internal validity of the model. As a result, this affected the comparison between the modelled strategies.

SeHCAT cannot be recommended for routine use in the NHS

4.15 The committee considered that there is an unmet clinical need for a test to diagnose bile acid diarrhoea. It recognised the value of having a diagnosis and access to treatment, but acknowledged that the evidence to support both the use of test and the treatment is highly uncertain. So, the full benefits and potential harms of widespread use of SeHCAT testing cannot be reliably quantified. There is no robust data to show the clinical utility of SeHCAT testing, that is:

- how well it predicts response to treatment

- how it influences clinical decision making
- the longer-term clinical outcomes with treatment.

Without this, SeHCAT's cost effectiveness cannot be adequately assessed. The committee concluded that it was unable to recommend the widespread use of SeHCAT testing. It encouraged further data collection to address the limitations in the evidence.

5 Recommendations for further research

5.1 Further research is recommended to understand how SeHCAT test results affect clinical decision making.

5.2 Further research is recommended to assess clinical outcomes after positive and negative SeHCAT test results. This research should focus on clinical outcomes relevant to people with chronic diarrhoea, such as severity of symptoms. Clinical outcomes should be measured in the short and long term.

5.3 Further research is recommended to assess the effectiveness of treatment options for bile acid diarrhoea. Consideration should be given to how well the treatments are tolerated and how they affect the severity of symptoms in the longer term.

5.4 Further research is recommended to better understand the health-related quality of life in people with bile acid diarrhoea. Consideration should be given to how quality of life differs before and after diagnosis, and how it is affected by treatment and symptom severity.

6 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

In addition NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for developing specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 5 into its guidance research recommendations database and highlight these recommendations to public research bodies.

7 Review

NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

Mark Kroese

Chair, diagnostics advisory committee

July 2021

8 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be assessed. If it is considered there is a conflict of interest, the member is excluded from participating further in that assessment.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

Specialist committee members

Matthew Brookes

Consultant gastroenterologist, Royal Wolverhampton NHS Trust

Fahmid Chowdhury

Consultant radiologist and nuclear medicine physician, Leeds Teaching Hospitals NHS Trust

Mark Follows

Clinical lead planned care / gastroenterology, Norfolk and Waveney CCG

Nigel Horwood

Lay specialist committee member

Yvonne McKenzie

Clinical dietitian, specialist in gastrointestinal nutrition and irritable bowel syndrome, independent

John McLaughlin

Professor of gastroenterology and nutrition, University of Manchester and Salford Royal Hospitals

Karen Slade

Lay specialist committee member

Peter Whorwell

Professor of medicine and gastroenterology, Wythenshawe Hospital

NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Suvi Härmälä

Topic lead

Rebecca Albrow

Technical adviser

Donna Barnes

Project manager

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