NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Report for Guidance Executive

Review of DG7: SeHCAT (tauroselcholic [75 selenium] acid) for the investigation of diarrhoea due to bile acid malabsorption in people with diarrhoea-predominant irritable bowel syndrome (IBS-D) or Crohn's disease without ileal resection.

This guidance was issued in November 2012.

The review date for this guidance is November 2015.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Recommendation

Transfer the guidance to the static guidance list.

That we should consult on the proposal.

A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper.

2. Original objective of guidance

To assess the clinical and cost effectiveness of SeHCAT for the investigation of diarrhoea related to bile acid malabsorption.

3. Current guidance

Adoption recommendations

1.1 SeHCAT (tauroselcholic [75 selenium] acid) is a potentially clinically important test for diagnosing bile acid malabsorption, which may be currently underdiagnosed. There is insufficient evidence to determine whether SeHCAT is a cost-effective option for diagnosing bile acid malabsorption in people with diarrhoea-predominant irritable bowel syndrome (IBS-D) and people with Crohn's disease without ileal resection. Therefore, for people with these conditions, SeHCAT is recommended for

use in research to collect evidence about its clinical benefits and risks and the acceptability associated with diagnosing and treating bile acid malabsorption.

Research recommendations

7.1 Research is needed to establish the validity and accuracy of the SeHCAT test and of any potential alternative technologies for measuring bile acid malabsorption in people with chronic diarrhoea diagnosed with IBS-D or Crohn's disease without ileal resection.

7.2 Research is needed to establish the nature of bile acid malabsorption and whether bile acid malabsorption is a primary or secondary condition in people diagnosed with IBS-D or Crohn's disease without ileal resection.

7.3 Research is needed to establish the efficacy and tolerability of bile acid sequestrants among people with IBS-D or Crohn's disease without ileal resection.

4. Rationale

No changes to the care pathway or the technology have been identified since the publication of diagnostics guidance 7. Further, no evidence has been found through the updated literature searches that will address the research recommendations or materially impact the recommendations made in diagnostics guidance 7. It is therefore proposed that this guidance is placed on the static guidance list.

5. Implications for other guidance producing programmes

No overlaps have been identified.

6. New evidence

The search strategy from the original diagnostics assessment report was re-run on Medline, Embase, Cochrane Library and the Science Citation Index. References from January 2012 onwards were reviewed. Additional searches of clinical trials registries and conference proceedings were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. Companies were asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. Specialist Committee Members for this guidance topic were also consulted and asked to submit any information regarding changes to the technology, the evidence base and clinical practice. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

6.1 Technologies

6.1.1 SeHCAT

Since the publication of DG7 there have not been any changes to SeHCAT.

6.1.2 Alternative technologies

No alternative technologies were included in DG7. Since its publication the following technologies have been proposed for the investigation of bile acid malabsorption:

- 14C glycocholate breath and stool test
- Serum C4
- Faecal bile acid
- Fibroblast growth factor 19

CE marked assays for 14C glycholate and faecal bile acids are available. Expert advice suggests that these alternative technologies are not currently in routine clinical use for the assessment and management of bile acid malabsorption.

6.2 Clinical practice

No changes to the diagnostic and care pathways that have occurred since the publication of DG7 have been identified. Literature searches suggest that SeHCAT may now be used for the investigation of bile acid malabsorption in people who have chronic diarrhoea after chemotherapy or radiotherapy treatment for cancer, however it is not certain if SeHCAT is in widespread clinical use for this indication.

6.3 New studies

19 studies were identified which met the inclusion criteria for the original systematic review; 18 primary studies and 1 systematic review. Of the 18 primary studies, all report responses to treatment with bile acid sequestrants following a SeHCAT test and 1 (Kumar et al. 2013) also reports the impact of SeHCAT testing on treatment plans. The systematic review and meta-analysis (Slattery et al. 2015) aimed to establish the prevalence of bile acid malabsorption in adults who met the Manning, Kruis, Rome I, II or II criteria for diarrhoea predominant irritable bowel syndrome. Bile acid malabsorption was diagnosed using a SeHCAT scan (<10% retention rate was used as the cut-off). In total, 6 studies which reported data for 908 people were included in the review. The rate of bile acid malabsorption ranged from 16.9% to 35.3% (pooled rate 28.1%).

6.3.1 Response to treatment

The data available on response to treatment following a SeHCAT scan are summarised below in table 1. The proportion of people with a positive SeHCAT scan varied between the studies, but is typically around 50%. The proportion of people reporting a good response to treatments showed greater variation between the studies, with 10 studies reporting a treatment response rate of 60% or less and 6 studies reporting a treatment response rate of greater than 70%. The variation in reported response rates could be because of heterogeneity in the study populations, that is they include both people with organic and functional diarrhoea, and differences in the threshold used to determine a positive SeHCAT scan. One study (Woolson et al. 2014) reported data for people with negative SeHCAT scans who were given bile acid sequestrants and only 1 person out of 63 reported a partial response compared to 52% of people with a positive SeHCAT scan who reported a good response. Fernandez-Banares et al. (2015) randomised people with a positive SeHCAT scan to either cholestyramine or placebo; no statistically significant differences in the percentage of people in clinical remission at week 8 were reported between the groups.

Table 1 Response to treatment following a SeHCAT scan

Study	Design	Population	Comparator	SeHCAT results[1]	Response to treatment
Aujla et al. (2014)	Retrospective cohort study	118 patients with chronic diarrhoea	None	51 people classed as having BAM 27/118 had severe BAM (<5% SeHCAT retention) 15/118 had moderate BAM (<10% SeHCAT retention) 9/118 had mild BAM (<15% SeHCAT retention	Data available for 68% (n=35) of the 51 people with BAM: 7 had colesevelam 28 had cholestyramine – 43% had a good response, 7% had a partial response and 25% had a poor response.
Bain et al. (2013)	Retrospective cohort study	122 patients referred for a SeHCAT scan	None	50% of people had a SeHCAT retention of <15%; 30 had <5% SeHCAT retention, 19 had 5.1%-10% SeHCAT retention and 12 had 10.1%-15% SeHCAT retention	84.9% of people with abnormal SeHCAT retention were treated with BAS and reported a good response.
Bajor et al. (2014)	Cohort study	141 patients with IBS	None	57 people had low SeHCAT retention <20%	27 people with low SeHCAT retention were treated with Colestipol and 55% reported successful treatment.
Dhaliwal et al. (2013)	Retrospective audit	286 patients with structural and functional IBS-D	None	286 people had a SeHCAT scan.	228 people received BAS and around 70% reported a good response to treatment.
Diana et al. (2013)	Retrospective audit	130 patients with structural and functional chronic diarrhoea	None	65 people had SeHCAT retention of <15% and were classed as having BAM	84% of people responded to BAS treatment. One third of people discontinued treatment, most commonly because of side effects.
Fernande z-Banares	Double-blind, randomised	26 people with chronic	None	All people have a SeHCAT 7 day retention of ≤20%	No statistically significant difference in clinical remission at week 8 between the

et al. (2015)	placebo-controlled, phase IV multicentre study	watery diarrhoea			cholestyramine and placebo groups.
Holmes et al. (2012)	Retrospective audit	55 people attending for SeHCAT scans	None	44 sets of notes could be analysed: 62% of scans were abnormal with SeHCAT retention of <15%, 32% had mild BAM, 24% had moderate BAM and 44% had severe BAM.	46% of people with BAM had a trial of treatment; 88% reported good response.
Kumar et al. (2013)	Retrospective audit	88 people referred for SeHCAT testing	None	56% of people were classed as having BAM (SeHCAT retention <15%); 59% had severe BAM, 18% had moderate BAM and 22% had mild BAM.	All people with abnormal SeHCAT scans and a subset (n=13) of people with normal SeHCAT scans received BAS. 55% of people with BAM reported a treatment response and 20% discontinued treatment because of side effects.
Kurien et al. (2014)	Retrospective cohort study	515 people referred for a SeHCAT scan	None	41% of people had BAM (SeHCAT retention <10%).	51% of people with BAM had BAS. Mean stool frequency decreased from 7.3 stools per day to 3.9 (p<0.0001). People who did not have treatment had no change in daily stool frequency.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maisterra et al. (2012)	Single centre observational study	84 people with IBS-D or functional diarrhoea	None	BAM diagnosed following a SeHCAT retention of <10%	82% of people receiving BAS had a complete response to cholestyramine, 15% had a partial response and 3% had a no response.
Mottacki et al.	Retrospective cohort	2112 people	None	BAM diagnosed following a SeHCAT retention of either <10%	People were excluded if no information from on the effect of treatment was available.

(2015)		referred for a SeHCAT scan with chronic diarrhoea		or <15%.	74% of people with BAM experienced symptomatic improvement on cholestyramine.
Notta et al. (2014)	Prospective cohort	78 people with chronic functional diarrhoea	None	A SeHCAT retention rate of <10% was considered abnormal. The initial SeHCAT scan was normal in 57% of people, and abnormal in 43%. After 3 months SeHCAT retention improved in 14/25 patients with complete response to BAS and in 3/5 people with partial response to BAS.	People with a positive SeHCAT scan had cholestyramine for 3 months; 74% reported a complete response, 15% a partial response and 2% no response. 9% discontinued treatment.
Orekoya et al. (2015)	Retrospective audit	264 people with chronic diarrhoea referred for a SeHCAT scan	None	139 people had a SeHCAT retention rate of <15% and were diagnosed with BAM.	123 people with BAM were given cholestyramine as a first line treatment, 56% of whom responded. People who did not report improvement were given second line colesevelam, which was better tolerated than cholestyramine.
Puig et al. (2012)	Cohort study	75 people with chronic diarrhoea	None	BAM was diagnosed where SeHCAT retention rate was <10%. 45% of patients had BAM – 28% had a retention rate of <5% and 17% had a retention rate of <10%.	57% of people with a SeHCAT retention rate of <5% needed high dose treatment compared to 38% of people with retention rates of <10%. 66% of people with a SeHCAT retention rate of <5% had complete response, 20% partial response and 4% no response. 85% of people with a SeHCAT retention rate of <10% had a complete response, and 15% a partial response.
Rizwan et al. (2013)	Retrospective audit	87 people with chronic diarrhoea	None	BAM was diagnosed where the SeHCAT retention rate was <15%. 50.1% of people had BAM; 63.6% had severe BAM (SeHCAT	78% of people with BAM were treated with BAS (colesevalam or cholestyramine). 70% of people reported good or partial response. 4 people discontinued cholestyramine

				retention <5%), 22.7% had moderate BAM (SeHCAT retention <10%) and 13.6% had mild BAM (SeHCAT retention <15%).	because of side effects.
Rojas et al. (2013)	Retrospective audit	297 people with chronic diarrhoea	None	A SeHCAT retention rate of <10% was considered abnormal. 44% of people had a SeHCAT retention rate of <10%.	113 people were treated with cholestyramine and 83% reported an improvement in symptoms.
Sarkodieh et al. (2013)	Retrospective audit	82 people having a SeHCAT scan.	None	A SeHCAT retention rate of <15% was considered abnormal. 62% of people had an abnormal SeHCAT result – 27% had mild BAM, 12% had moderate BAM and 23% had severe BAM.	49% of people with an abnormal SeHCAT result had BAS; 42% reported improvement in symptoms and 8% reported side effects.
Woolson et al. (2014)	Retrospective audit	121 people having a SeHCAT scan	None	Off the whole population receiving the test: 78% had a previous colonoscopy 33% had a previous oesophago-gastro-duodenoscopy 21% had a previous CT scan 47% of people had a positive SeHCAT scan (cut-off not reported) Crohn's disease and right hemicolectomies were significantly associated with BAM.	83% of people with a positive SeHCAT scan were given BAS: 52% reported a good response 23% reported no response 10% could not tolerate the treatment 63 people with a negative SeHCAT scan were given BAS: 1 person reported a partial response
BAM = bile acid malabsorption; BAS = bile acid sequestrants					

6.3.2 Impact of SeHCAT scan on treatment decisions

Kumar et al. (2013) report data on the impact of SeHCAT on treatment decisions. In a retrospective audit of 88 people having a SeHCAT scan (further details provided above in table 1). SeHCAT changed treatment in 84% of people with an abnormal scan and 33% of people with a normal scan.

7. Summary of new evidence and implications for review

No evidence has been found which could have a material impact on the recommendations in the published guidance. No changes to the technology, or to the care pathway for people with diarrhoea predominant irritable bowel syndrome or Crohn's disease without ileal resection have been identified since the publication of diagnostics guidance 7. In the majority of studies found by the updated literature searches, treatment with bile acid sequestrants and follow-up was given only to those with a positive SeHCAT scan which limits the conclusions which can be drawn regarding the validity and accuracy of SeHCAT. It is therefore unlikely that this uncertainty can be addressed at present. Further, given the limited information on treatment following a negative SeHCAT scan, and with the majority of studies not including a placebo arm, there is insufficient evidence to address the uncertainties relating to the efficacy of bile acid sequestrants in people with diarrhoea predominant irritable bowel syndrome or Crohn's disease without ileal resection.

Some evidence is available to suggest that SeHCAT scans could be used to determine whether bile acid malabsorption is present in people with chronic diarrhoea following chemotherapy or radiotherapy for cancer. However, there is no evidence to suggest that SeHCAT is being routinely used in this population in the NHS and the population is outside the scope of the guidance.

8. Implementation

Expert advice suggests that SeHCAT is currently being used in the NHS.

9. Equality issues

It was noted that people with chronic diarrhoea are likely to be classified as having a disability and therefore be protected under the Equality Act 2010.

GE paper sign off: Carla Deakin, 4 January 2016

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Appendix 1 – explanation of options

If the published Diagnostics Guidance needs updating NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
Standard update of the guidance	A standard update of the Diagnostics Guidance will be planned into NICE's work programme.	No
Accelerated update of the guidance	An accelerated update of the Diagnostics Guidance will be planned into NICE's work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Diagnostics Guidance does not need updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Diagnostics Guidance on the static list should be flagged for review.	Yes
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE's work programme.	No
Defer the decision to review the guidance to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Diagnostics Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care (updated 2015) NICE guidelines CG61

Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy (2015) NICE technology appraisal guidance TA352

Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel (2013) NICE diagnostics guidance DG11

Crohn's disease: Management in adults, children and young people. (2012) NICE guidelines CG152

Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (2011) NICE guidelines CG118

Infliximab (review) and adalimumab for the treatment of Crohn's disease (2010) NICE technology appraisal guidance TA187

Diarrhoea and vomiting in children: Diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years (2009) NICE guidelines CG84

Extracorporeal photopheresis for Crohn's disease (2009) NICE interventional procedure guidance IPG288

Irritable bowel syndrome (2015) NICE Pathway

Crohn’s disease (2015) NICE Pathway

Diarrhoea and vomiting in children (2015) NICE Pathway

Bile acid malabsorption: colesevelam (2013) NICE advice ESUOM22

Acute diarrhoea in children: racecadotril as an adjunct to oral rehydration (2013) NICE advice ESNM12

Acute diarrhoea in adults: racecadotril (2013) NICE advice ESNM11

Irritable bowel syndrome with constipation in adults: linaclotide (2013) NICE advice ESNM16

In progress

Crohn's disease - Tests for therapeutic monitoring of TNF inhibitors (LISA-TRACKER ELISA kits, TNFa-Blocker ELISA kits, and Promonitor ELISA kits). NICE diagnostic guidance. Expected publication date: December 2015

Crohn's disease - management in adults, children and young people (standing committee update). NICE guideline. Expected publication date: May 2016

Irritable bowel syndrome in adults. NICE Quality Standard. Expected publication date: February 2016

Details of new technologies

See section 6.1.2.

Registered and unpublished trials

Trial name and registration number	Details
The FOCCUS study: "Focusing on Cancers Chemotherapys' Untreated Symptoms" NCT02121626	To quantify the incidence, severity, frequency, impact on quality of life, and, where possible, the cause of the full range of chemotherapy-induced GI symptoms. Outcomes: Incidence of new onset GI symptoms per chemotherapy regimen Completion: Dec 2017
Assessment of BAM as a cause of chronic diarrhoea	To evaluate patients with functional chronic diarrhoea, and to estimate the proportion of cases of bile acid malabsorption in these patients. Outcomes: To estimate proportion of cases of BAM in patients with functional chronic diarrhea & creation of a computer database with demographic, clinical and test results. Completion: March 2017

Trial name and registration number	Details
Use of SeHCAT to investigate the aetiology of chronic diarrhoea in patients with Crohn's disease after resection surgery	The primary aim is to establish the usefulness of SeHCAT to diagnose malabsorption of bile acids in Crohn's disease patients after resection surgery. The second aim is to determine the usefulness of the test in guiding therapy. Outcomes: To determine the diagnostic yield of SeHCAT in patients with Crohn's disease after surgery, after exclusion of active disease by appropriate imaging methods. Completion: Dec 2016
Impact of rifaximin therapy on bile acid absorption in patients with diarrhoea-predominant irritable bowel syndrome or functional diarrhoea.	To determine whether a 14-day course of oral rifaximin at 400 mg TID affects SeHCAT retention in patients with diarrhoea-predominant IBS or functional diarrhoea Outcomes: Variation (∆) in the mean SeHCAT retention 4 weeks after rifaximin treatment. Completion: March 2016
Prospective assessment of SeHCAT retention before and after cholecystectomy	To ascertain the effect of cholecystectomy surgery on SeHCAT retention Outcomes: Prevalence of abnormal SeHCAT scans before and after Cholecystectomy Completion: August 2016
The effectiveness of gastrointestinal intervention during pelvic chemoradiotherapy: A randomised controlled pilot study	To determine if a gastrointestinal care bundle, incl. nutritional intervention and detecting and treating lactose intolerance, small bowel overgrowth and BAM, improves GI symptoms in the short-term. Outcomes: Gastrointestinal symptoms as determined by CTCAE pelvic symptom questionnaire immediately post-treatment (week 6). Completion: August 2016

Trial name and registration number	Details
Characterising the Provision of SeHCAT Services in the United Kingdom: A Multi-Centre Prospective Survey (KiTEC)	Survey for patients referred for SeHCAT scan Outcomes: Characterising the provision of SeHCAT service in UK Completion: Patient recruitment was completed in May 2015, awaiting analysis
Audit SeHCAT (Chelsea and Westminster Hospital, Royal Marsden Hospital)	Outcomes: 4 year follow up after SeHCAT Completion: Data collection till July 2016
A double-blind, randomized, placebo-controlled, study to demonstrate the efficacy and safety of 250 mg or 1 g A3384 administered orally twice daily for two weeks to patients with BAM EUCTR2013-002924-17-SE	Double-blind, randomized, placebo-controlled A new drug for patients with BAM (A3384). A SeHCAT 7 day retention of less than 10% is required for inclusion in the study Primary outcome: change from baseline in number of bowel movements during the 2nd treatment week. Completion: unknown

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