NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

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

Final scope

November 2020

1 Introduction

In January 2020, following the Diagnostics Guidance review proposal process, it was determined that NICE diagnostics guidance 7 on SeHCAT for the investigation of chronic diarrhoea due to bile acid malabsorption should be updated. During the development of the review proposal it was identified that a substantial amount of new evidence has become available and there have been changes to the care pathway, therefore a standard update to the guidance is needed.

The final scope was informed by discussions at the scoping workshop held on 22 October 2020 and the assessment subgroup meeting held on 4 November 2020. A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technology

This section describes the properties of the diagnostic technology based on information provided to NICE from the manufacturers and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

SeHCAT (tauroselcholic [75 selenium] acid) is a radiopharmaceutical capsule for diagnostic use. It is indicated for the investigation of bile acid malabsorption and measurement of bile acid pool loss. It may be also be used in the assessment of ileal function, in the investigation of inflammatory bowel disease and chronic diarrhoea and in the study of enterohepatic circulation (these uses are outside of the current scope). SeHCAT is manufactured by GE Healthcare.

Bile acid diarrhoea may currently be an underdiagnosed condition. When the condition is not investigated, people with bile acid diarrhoea may go through several unnecessary investigations and treatments for other conditions without improvement in symptoms. A positive SeHCAT test could result in people having earlier access to medication which may improve their quality of life. The use of SeHCAT may also reduce unnecessary investigations and treatments.

2.2 Product properties

SeHCAT is a diagnostic radiopharmaceutical capsule used to measure how well the body absorbs bile acids. The capsule contains 75 Selenium (a gamma-emitter) and a synthetic version of bile acid (tauroselcholic acid). When swallowed, SeHCAT is absorbed by the body like a natural bile acid. It can be detected in the body using a gamma camera.

A SeHCAT test involves 2 outpatient appointments in the nuclear medicine department of a hospital. During the first appointment, the patient swallows a SeHCAT capsule, waits for up to 3 hours and a baseline scan is taken. During the second appointment on the seventh day after the first appointment, a follow-up scan is taken. It may be considered reasonable to stop any anti-diarrhoeal medication for the duration of the test as there is a possibility that this may interfere with the test result.

The result of the test shows how much SeHCAT remains in the body. To calculate the result, the amount of radioactivity detected in the follow-up scan is divided by the amount of radioactivity detected in the baseline scan.

Diagnosis of bile acid diarrhoea is typically made when around 15% or less of SeHCAT remains in the body. Because the SeHCAT results are on a continuous scale, the threshold used for a positive result can vary. But usually retention values above 20% are not considered indicative of bile acid diarrhoea.

Clinicians also use SeHCAT results to grade the severity of the condition:

- retention values from 10% to 15% indicate mild bile acid diarrhoea
- retention values from 5% to 10% indicate moderate bile acid diarrhoea
- retention values from 0% to 5% indicate severe bile acid diarrhoea.

There is no paediatric dosage form or clinical experience of the use of SeHCAT in children. The same dosage as in adults is used. A careful

assessment of risk/benefit ratio should be done before use of the product in children.

2.3 Potential alternative technologies

Current British Society of Gastroenterology (BSG) guidelines for the investigation of chronic diarrhoea in adults (Arasaradnam et al. 2018) recommends that where SeHCAT is not available, serum C4 test, serum FGF19 test or faecal bile acid test (in the UK, IDK Bile Acids, a single-stool sample faecal bile acids test manufactured by Immundiagnostik AG, is commercially available through Biohit) may be used for diagnosing bile acid diarrhoea.

Like SeHCAT, these tests aim to provide a picture of how the bile acid recycling system functions. However, in these tests, this picture is produced over a much shorter period of time than during SeHCAT test (in the case of C4 and FGF19 tests at a single point in time). Because of this, the test results may vary more when eating patterns are changed or depending on the time of day the sample for the test is taken.

These tests will not be included in the assessment because stakeholders informed NICE that they are not currently in use in the NHS and clinical interest in using these tests is limited.

3 Target condition

3.1 Bile acid diarrhoea

Bile acid diarrhoea is a form of chronic diarrhoea. In bile acid diarrhoea, the recycling of bile acids in the body is not functioning properly. Bile acids are produced by the liver and stored in the gallbladder until they are released into the small intestine to aid digestion. Usually, bile acids are reabsorbed into the liver in the final section of the small intestine. If they are not reabsorbed or the body produces more bile acid than can be reabsorbed, excess amounts of bile travels from the small bowel to the colon, stimulates salt and water secretion and bowel movements and results in diarrhoea.

Symptoms of bile acid diarrhoea may include explosive, smelly or watery diarrhoea, urgency in going to the toilet, abdominal pain, swelling or bloating and faecal incontinence.

The most common form of bile acid diarrhoea is caused by overproduction of bile acid in people with no physical damage to the bile acid recycling system. This primary form of bile acid diarrhoea is often missed as a cause of chronic diarrhoea. Due to the similarity in symptoms between bile acid diarrhoea and

both IBS-D and functional diarrhoea, bile acid diarrhoea may be misdiagnosed. The actual cause of diarrhoea in up to a third of people with suspected IBS-D or functional diarrhoea may be bile acid diarrhoea. About 500,000 people in the UK are estimated to have primary bile acid diarrhoea.

Bile acid diarrhoea can also appear as a secondary condition after the small bowel or another part of the bile acid recycling system has been damaged by disease, surgery, or a certain type of treatment. Bile acid diarrhoea has been reported in Crohn's disease, and after gall bladder removal, pelvic and abdominal radiotherapy and after chemotherapy for cancer.

3.2 Diagnostic and care pathway

3.2.1 Diagnosis

Diagnosis of bile acid diarrhoea requires more than one investigation. Initial investigations should involve history taking, an assessment of clinical symptoms and signs to exclude cancer (NICE's guideline on recognition and referral for suspected cancer). Blood and stool tests to exclude anaemia, coeliac disease, infection and inflammation should be performed (BSG guidelines for investigation of chronic diarrhoea in adults [Arasaradnam et al. 2018], NICE's guidance for faecal calprotectin diagnostic tests for inflammatory diseases of the bowel). These initial investigations often take place in primary care.

Referral to secondary care is required for investigation and diagnosis of bile acid diarrhoea. SeHCAT is recommended as the preferred diagnostic test in the BSG guidelines for investigation of chronic diarrhoea in adults (Arasaradnam et al. 2018). It is recommended that bile acid diarrhoea is investigated in all cases of persistent chronic diarrhoea without a known cause.

When IBS-D or functional diarrhoea is suspected or has been previously diagnosed, bile acid diarrhoea should also be investigated. NICE's guidelines for diagnosis and management of irritable bowel syndrome recommend considering a diagnosis of irritable bowel syndrome (IBS) when the initial investigations are normal and certain symptoms are present. No further tests such as colonoscopy or imaging are necessary to confirm an IBS diagnosis.

Investigation of bile acid diarrhoea may also be considered when diarrhoea persists regardless of conventional treatment in those conditions where it may appear as a secondary condition. But experts suggested that when chronic diarrhoea appears after ileal resection (removal of the terminal part of the small bowel to treat Crohn's disease), bile acid diarrhoea is so common (more

than 95% of cases) that a diagnostic test before beginning treatment is not necessary. Similarly, when chronic diarrhoea follows gall bladder removal, or abdominal or pelvic radiotherapy or chemotherapy for cancer, clinicians have a high suspicion of bile acid diarrhoea and a diagnostic test before starting the treatment may not be needed.

Current clinical practice seems to vary and differ from the recommended diagnostic pathway. Studies on SeHCAT use and on patient experience indicate that imaging tests and invasive investigations such as colonoscopy are often performed before the SeHCAT scan (Fernandes et al. 2019, Summers et al. 2016, Turner et al. 2017). Multiple interactions with different clinicians over many years often take place before bile acid diarrhoea is investigated (Bannaga et al. 2016).

The manufacturer advises that SeHCAT testing is currently available at 85 hospitals across 74 of 225 NHS acute trusts in England (data from August 2020). According to the 2018-2019 NHS National Cost Collection data, the trusts with SeHCAT testing perform about 10,000 SeHCAT tests per year (some clinicians estimate closer to 20,000 tests per year). The number of tests performed in different trusts ranges widely from less than 50 tests per year to more than 500 tests per year.

3.2.2 Treatment

After diagnosis, symptoms of bile acid diarrhoea are most often controlled with bile acid sequestrant medication. Bile acid sequestrants bind to bile acids in the small bowel and prevent them from irritating the colon. They may also slow down the transit of bile acids through the bowel. The treatment is likely to be long term.

There are currently 3 bile acid sequestrants available: colestyramine, colestipol and colesevelam. Colestyramine and colestipol come in powder or granule form and colesevelam in tablet form. Use of both colestipol and colesevelam for bile acid diarrhoea is currently off-label (NICE's evidence summary on use of colesevelam for treatment of bile acid diarrhoea). Ease of access to colesevelam in primary care varies from region to region. Bile acid sequestrants are not always easy to tolerate. Constipation and flatulence are very common side effects. Some people find the taste and texture of colestyramine and colestipol very unpleasant. Some have reported gaining weight.

Treatment often starts with colestyramine, except in Crohn's disease where colesevelam is often tried first. However, the initial treatment plan may sometimes need modification. Common changes include increasing the dose

(finding a suitable dose may take up to 12 weeks), adding anti-diarrhoea medication such as loperamide to the treatment, changing to an alternative bile acid sequestrant and introducing dietary changes (Walters et al 2020, British Dietetic Association guidelines for the dietary management of irritable bowel syndrome in adults [McKenzie et al. 2016]). A low-fat diet alone may also potentially lead to improvement of bile acid diarrhoea symptoms. Supplements of vitamins A, D, E, K, and folic acid may be required both with a long-term bile acid sequestrant therapy (Canadian Association of Gastroenterology guideline on the management of bile acid diarrhea [Sadowski et al. 2020]) and a low-fat diet.

In current practice, in some Trusts, bile acid sequestrant treatment of bile acid diarrhoea is started without a diagnostic test being performed (trial of treatment). Trial of treatment may take between 4 and 12 weeks.

3.3 Patient issues and preferences

Bile acid diarrhoea is a long-term condition. In addition to the physical symptoms, issues relating to well-being and mental health such as embarrassment, being nervous about leaving home, depression, isolation, feeling helpless and low self-esteem are common. Patients have reported a lack of awareness of bile acid diarrhoea among clinicians.

During the SeHCAT test, people receive a small dose of radiation from the SeHCAT capsule. Although the level of radiation is low, people may be worried. Information about the radiation exposure should be provided in advance of the test.

Use of SeHCAT may lead to earlier access to appropriate treatment and improvement in quality of life for people who have a positive test result. It may also help avoid unnecessary referrals for other diagnostic procedures such as imaging or invasive procedures such as colonoscopy. This would save people additional trips to the hospital, time off work and anxiety about the hospital procedures.

Prescribing bile acid sequestrant treatment without performing a diagnostic test may lead to even earlier access to appropriate treatment (a typical waiting time to have a SeHCAT test is 6 weeks). Currently, because of COVID-19, outpatient appointments may be delayed and both options should be discussed (NICE's COVID-19 rapid guideline: arranging planned care in hospitals and diagnostic services). Some people may prefer not to wait for the diagnostic test and trial the treatment instead. However, some may prefer to receive a formal diagnosis based on a diagnostic test result before committing to treatment that may not be easy to tolerate.

4 Comparator

No reference standard for SeHCAT currently exists. To estimate the accuracy of the test, response to bile acid sequestrant treatment is used. There is therefore no commonly used direct comparator for the SeHCAT test. When a diagnostic test is not available and there is no history that would raise suspicions of secondary bile acid diarrhoea, bile acid diarrhoea is often misdiagnosed and treated as IBS-D. In some Trusts, when either primary or secondary bile acid diarrhoea is suspected, prescribing a trial of bile acid sequestrant treatment without a diagnostic test is current practice.

5 Scope of the assessment

Table 1 Scope of the assessment

Decision question	What is the clinical and cost effectiveness of SeHCAT for the investigation and diagnosis of bile acid diarrhoea?
Populations	• Adults presenting with chronic diarrhoea with an unknown cause, suspected or diagnosed IBS-D or functional diarrhoea (potential primary bile acid diarrhoea) • Adults with Crohn's disease (without ileal resection) presenting with chronic diarrhoea (potential secondary bile acid diarrhoea)
Intervention	SeHCAT test
Comparators	• No testing and no treatment for bile acid diarrhoea. • No testing and trial of treatment for bile acid diarrhoea.
Healthcare setting	Secondary care
Outcomes	Intermediate measures for consideration may include: • Predictive accuracy (ability of the test to predict response to treatment, proxy measure of diagnostic accuracy) • Time to test result • Impact of test result on clinical decision-making • Impact of test result to adherence to treatment • Response to treatment • Use of further tests • Adverse events (during or after testing)
	Clinical outcomes for consideration may include: • Morbidity

	• Mortality
	Patient-reported outcomes for consideration may include: • Health-related quality of life • Acceptability of test (such as anxiety about the testing procedure, acceptability of time to test result) • Side effects of testing (this may also include health effects of stopping any anti-diarrhoeal medication for the duration of the test) • Side effects of treatment
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Cost of testing for bile acid diarrhoea • Cost of further tests • Cost of treatment and follow-up
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year (ICER).
Time horizon	The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

6 Other issues for consideration

6.1 Use of SeHCAT in the UK

Use of SeHCAT in clinical practice seems to differ from the recommended diagnostic pathway. Imaging tests and invasive investigations such as colonoscopy are often performed before the SeHCAT test (Fernandes et al. 2019, Summers et al. 2016, Turner et al. 2017) and multiple interactions with different clinicians over many years often take place before bile acid diarrhoea is investigated (Bannaga et al. 2016).

6.2 Test accuracy and response to treatment

Because no reference standard for SeHCAT currently exists, the ability of the test to predict response to treatment will be used to estimate the accuracy of the test (predictive accuracy). Any improvement of symptoms of bile acid diarrhoea (such as disappearance of diarrhoea or reduction in bowel movements) may be considered as response to treatment.

6.3 Treatment

There is some evidence that dietary changes may improve symptoms of bile acid diarrhoea. A recent survey of clinical expert practice also suggests that dietary changes may be considered as part of the treatment (Walters et al. 2020). The impact of dietary changes may need to be considered in the analysis.

6.4 Approach to modelling cost-effectiveness

The evidence for the assessment would ideally come from randomised or non-randomised controlled trials that follow patients from testing, through treatment, to final outcomes. It is unlikely that these “end-to-end” studies will be available, and a linked-evidence approach may be needed for the economic model.

7 Potential 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.

People with chronic diarrhoea may be classified as having a disability and therefore be protected under the Equality Act 2010. IBS is twice as common in women as in men. It may be that the prevalence distribution of bile acid diarrhoea follows a similar pattern. Symptoms of bile acid diarrhoea often first appear between the age of 20 and 30 years. Less people from black, Asian and minority ethnic groups than expected are seen for investigation of bile acid diarrhoea. People who are pregnant, breast feeding or considering maternity may need to delay attending the diagnostic test because the test involves exposure to radiation.

8 Potential implementation issues

SeHCAT is currently in routine clinical use in many NHS acute trusts. The test has a healthcare resource group code (RN14Z) and an NHS Tariff for administering the test. The equipment used for taking the scan is used also in other common nuclear medicine procedures and is widely available in nuclear medicine departments. The adoption of the test does not require extensive additional training.

8.1.1 "No demand"

In a 2012 survey of 129 nuclear medicine departments in the UK, one of the most common reasons for not offering SeHCAT testing was "no demand from local clinicians" (Smith et al. 2013). While this survey is somewhat old, current use of trial of treatment without a diagnostic test may still mean that clinicians are not asking for SeHCAT service to be offered. Patients have also reported a lack of awareness of the condition among clinicians.

8.1.2 Facilities and commissioning

There are logistic considerations for high-throughput nuclear medicine departments as other concurrent studies may result in background radiation which could affect SeHCAT testing. For nuclear medicine departments that are running at or close to capacity in terms of staff or equipment or both, additional funding may be required to increase capacity.

9 Authors

Suvi Härmälä
Topic Lead

Peter O'Neill
Technical Adviser

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Appendix A Glossary of terms

Bile acid diarrhoea
A form of chronic diarrhoea. In bile acid diarrhoea, the recycling of bile acids in the body is not functioning properly. Excess amount of bile travels from the small bowel to the colon, stimulates salt and water secretion and bowel movements and results in diarrhoea.

Bile acid malabsorption
Alternative term for bile acid diarrhoea.

Bile acid sequestrants
Medication for the treatment of bile acid diarrhoea symptoms.

Chronic diarrhoea
Chronic diarrhoea is the persistent alteration from the norm with stool consistency between types 5 and 7 on the Bristol stool chart and increased frequency greater than 4 weeks' duration (BSG guidelines for investigation of chronic diarrhoea in adults [Arasaradnam et al. 2018]).

Diarrhoea-predominant irritable bowel syndrome (IBS-D)
A symptom profile in IBS characterised by chronic diarrhoea (please see also irritable bowel syndrome below). This is the most common IBS symptom profile.

Functional diarrhoea
Functional diarrhoea is a type of chronic diarrhoea where no structural or biochemical abnormalities have been identified as a cause for the symptoms in people who do not meet the symptom profile for IBS.

Incremental cost-effectiveness ratio (ICER)
The difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest

Irritable bowel syndrome (IBS)
A chronic, relapsing and often life-long disorder. IBS is characterised by the presence of abdominal pain or discomfort, which may be associated with defaecation and/or accompanied by a change in bowel habit. Symptoms may include constipation or diarrhoea or both and abdominal distension, usually referred to as bloating. Symptoms sometimes overlap with other gastrointestinal disorders.

Linked-evidence approach
Methodological approach used for modelling of cost and consequences of a diagnostic test when no evidence that directly estimates this is available. In linked-evidence approach, evidence from diagnostic outcome studies is combined with evidence from clinical outcome studies.

Predictive accuracy
Ability of a test to predict a future outcome such as response to treatment. To assess this, predictive accuracy studies use an accuracy-type study design. But because predictive accuracy studies do not account for other potential predictors of the outcome (they are not true prediction modelling studies), their results may not reflect the true predictive ability of the test.

Quality-adjusted life year (QALY)
A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.

Reference standard
The best currently available diagnostic test, against which the technology under assessment is compared.

SeHCAT
A radiopharmaceutical that is licensed for use in the investigation of bile acid malabsorption and measurement of bile acid pool loss.

Appendix B Abbreviations

BSG	British Society of Gastroenterology
IBS	Irritable bowel syndrome
IBS-D	Diarrhoea-predominant irritable bowel syndrome
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence

Appendix C References

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Appendix D Product properties

Additional details on the product properties are available in the following documentation:

SeHCAT: Summary of SeHCAT product characteristics

IDK Bile Acids test: IDK Bile Acids Test product manual