Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Assessment

November 2023

In response to an enquiry from the Modernising Patient Pathways Programme

Capsule sponge technologies for the detection of Barrett's oesophagus and early stage oesophageal cancer

Key messages

1. Capsule sponge technologies are potentially an alternative or precursor to endoscopy for diagnosing Barrett's oesophagus or early stage oesophageal cancer.
2. Using capsule sponge testing as a triage tool has been shown to facilitate access to endoscopy for patients who are at the greatest risk of a clinically significant diagnosis and reduce endoscopy waiting lists.
3. Capsule sponge technologies are likely to misdiagnose approximately 28% of patients tested. Endoscopy has been reported to miss between 21% and 23.5% of early oesophageal cancers in patients with Barrett's oesophagus.
4. The majority of patients asked found capsule sponge testing an acceptable alternative to endoscopy.
5. A budget impact model for the NHS found that the use of capsule sponge testing for patients with chronic reflux symptoms referred for an endoscopy led to resource savings.
6. Please note that all the evidence on capsule sponge technologies relates to the Cytosponge™ device which is no longer used in NHSScotland.

What were we asked to look at?

We were asked to evaluate the use of capsule sponge devices to detect Barrett's oesophagus and early stage oesophageal cancer. We considered clinical effectiveness, cost effectiveness, safety and the patient experience.

Why is this important?

The majority of people diagnosed with oesophageal cancer in Scotland present with advanced disease.[1] Early detection of oesophageal cancer is associated with improved survival. Patients with early stage oesophageal cancer have a 5-year survival rate of approximately 95% compared with 5–40% in patients with advanced disease at diagnosis.[2]

Chronic gastro-oesophageal reflux (GORD) and Barrett's oesophagus are known risk factors for developing oesophageal cancer.[2, 3] People with chronic reflux often undergo endoscopies to detect Barrett's oesophagus.[4] People with Barrett's oesophagus undergo routine surveillance endoscopies to detect early signs of cancer.[1, 3] The majority of people with chronic reflux or Barrett's oesophagus do not progress to having cancer. Providing endoscopies for these two patient groups contributes to a high demand on endoscopy services.

During the COVID-19 pandemic many endoscopies were cancelled, resulting in long patient waiting lists.[5] The Scottish Government recognised the potential for capsule sponge technologies to improve patient access to cancer diagnosis and reduce endoscopy waiting times.[6, 7]

What was our approach?

We reviewed the published literature on the clinical effectiveness, cost effectiveness, safety and patient experience of capsule sponge technologies. We conducted a budget impact analysis based on national adoption of capsule sponge technologies to detect Barrett's oesophagus in people with GORD who are on an endoscopy waiting list. We analysed data collected in Scotland to inform the use of capsule sponge technologies.

More information about SHTG assessments can be found on our website.

What next?

Our assessment will be included in an Accelerated National Innovation Adoption (ANIA) value case, which will be used by the Innovation Design Authority to inform their decision about the potential for a national 'business as usual' capsule sponge testing service.

Key findings from the evidence

All of the evidence on capsule sponge technologies relates to the Cytosponge™ device.

Clinical effectiveness

People with chronic reflux symptoms

1. A pooled estimate of diagnostic accuracy (six studies, n=1,957) found that Cytosponge™ has a sensitivity of 81% (range 71.4% to 90.9%) and a specificity of 91% (range 90.3% to 94.0%) for the detection of Barrett's oesophagus. In other words, 19% of people tested for Barrett's oesophagus using Cytosponge™ would receive a false negative result and 9% a false positive result.

2. In the BEST3 randomised controlled trial (RCT) the estimated cumulative rate of Barrett's oesophagus at 12 months was 20.2 per 1,000 person-years in the capsule sponge group and 2.0 per 1,000 person-years in the usual care group [risk ratio adjusted for cluster randomisation 10.6 (95% confidence interval (CI) 6.0 to 18.8].

3. In an observational study (n=4,456) assessed using Cytosponge™ to triage patients who had been referred for an endoscopy.
    - 1.6% of patients were positive for cellular changes (atypia), tumour protein biomarkers (p53) or both, were considered high risk and were referred for an urgent endoscopy
    - 12.9% of patients were positive for the trefoil factor 3 (TFF3) biomarker but negative for atypia and p53, and were referred for routine endoscopy
    - 85.6% of patients tested negative for TFF3, p53 and atypia, and did not receive an endoscopy.

Patients with Barrett's oesophagus under surveillance

4. In a cross-sectional study (n=334), Cytosponge™ had a sensitivity of 89% and a specificity of 84% for detecting high grade dysplasia or early oesophageal cancer. This means that 11% of patients would receive a false negative result and 16% would receive a false positive result.

5. Two observational studies (n=6,121 and n=223) assessed using Cytosponge™ to triage patients for endoscopy. Patients were categorised as at high, moderate or low risk of developing oesophageal cancer based on their Cytosponge™ results:
    - in one study, 8.7% of patients were considered high risk and referred for an urgent endoscopy. 28.7% of patients were moderate risk and referred for routine endoscopy. 62.6% were low risk and did not receive an endoscopy
    - in the second study, 17% of patients were referred for an urgent endoscopy based on a high risk of cancer. Another 17% were considered moderate risk and referred for routine endoscopy. 65% were low risk and did not receive an endoscopy.

NHS data analysis: patients with chronic reflux or Barrett's oesophagus

6. In our evaluation of data from NHSScotland:
    - most Cytosponge™ procedures collected enough oesophageal cells for testing in patients with chronic reflux (89.75%) or Barrett's oesophagus (89.15%)
    - for high risk patients with Barrett's oesophagus under surveillance (n=299), the average time from last endoscopy to treatment (1,538 days) was longer than the time from Cytosponge™ to treatment (244 days).

7. An unpublished analysis of Scottish data found that patients considered high risk for oesophageal cancer (n=271) received an endoscopy within a median of 2 months after their Cytosponge™ test. Overall, introducing Cytosponge™ led to a 4 month reduction in delays for patients awaiting a surveillance endoscopy.

8. NHS England evaluated Cytosponge™ triage of patients waiting for investigation of chronic reflux symptoms. The majority of patients (78%, n=1,694) who completed the test were removed from the endoscopy waiting list.

Safety

9. Serious adverse events associated with capsule sponge devices include the string breaking and oesophageal bleeding after withdrawal of the device. Few serious adverse events were reported in published studies.
    - Between December 2022 and June 2023, 13 patients worldwide (five from Scotland) reported the Cytosponge™ device became detached from the string during their procedure. All patients underwent an urgent endoscopy to retrieve the sponge from the stomach or oesophagus without further adverse consequences.
    - In June 2023, the Medicines and Healthcare Products Regulatory Agency (MHRA) announced the immediate recall of 15 batches of Medtronic Cytosponge™ devices.

The devices in these batches were at increased risk of the sponge detaching from the string during a procedure.

10. Other adverse events associated with capsule sponge testing include a sore throat (4%), indigestion or reflux (19%) and oesophageal or gastric pain (15%).

11. A small proportion of patients in most studies (approximately 3.5%) were unable to swallow the Cytosponge™. Failure to swallow the sponge was more common in patients with Barret's oesophagus (5.7%) compared with patients who have reflux (2.1%).

Patient and social aspects

12. One study (n=1,488) found high levels of patient satisfaction with their experience of the Cytosponge™ test, with 80% of patients willing to have the test again. Successfully swallowing and withdrawing the capsule sponge device caused the most concern. Patients were more likely to have a poor experience if they had high anxiety, were unable to swallow the sponge or drank alcohol on most days.

13. In a pooled analysis of five studies (n=2,289), Cytosponge™ was more acceptable to patients than endoscopy without sedation, but less acceptable than endoscopy with sedation.

14. Two studies exploring the views of the public on Cytosponge™ found that the main concern was the risk of gagging or vomiting during the test.

Cost effectiveness

Patients with chronic reflux symptoms in a primary care setting (screening)

15. Three economic analyses compared screening using Cytosponge™ plus TFF3 testing with no screening or usual care for detecting Barrett's oesophagus.
    - All three analyses concluded that screening using Cytosponge™ plus TFF3 testing was more costly but more effective than no screening or usual care over a lifetime time horizon.
    - Two analyses reported a very high likelihood (≥94%) of screening using Cytosponge™ plus TFF3 testing being cost effective from an NHS perspective when compared with no screening.
    - Results were sensitive to the prevalence of Barrett's oesophagus, estimates of health-related quality of life, the effectiveness of radiofrequency ablation and the total cost of a Cytosponge™ procedure.

Patients with chronic reflux symptoms in secondary care

16. A service evaluation in NHS England concluded that using Cytosponge™ as a triage tool for patients with low risk reflux symptoms referred for an endoscopy was moderately less costly (-£421.57 per patient) but marginally less effective [-0.0041 quality adjusted life-years (QALYs) per patient] than usual care.

17. The base case results of our budget impact analysis comparing capsule sponge testing with usual care in patients with chronic reflux symptoms referred for an endoscopy, estimated an incremental cost saving of £0.7 million in year 1, rising to £3.3 million in year 5.
    - With 100% uptake of capsule sponge testing, an estimated 20,000 fewer endoscopy procedures would be needed per year.
    - Capsule sponge testing is not expected to provide cash releasing savings of this magnitude during the 5-year period considered because the majority of resources included in these figures, such as staff and endoscopy equipment costs, are expected to be fixed over the short term.

Contents

Definitions

Atypia: the presence of one or more cell features that differ from a normal appearing cell or group of cells on histological examination.[8] The terms atypia and dysplasia may be used interchangeably.

Dysplasia: the abnormal development of cells, tissues or structures in the body.[9] In the oesophagus, dysplasia is defined as normal, flat squamous cells becoming more like the columnar shaped cells found in the lining of the stomach or bowel.[3] High grade dysplasia refers to more severely abnormal cells that are immediately pre-cancerous.[10]

Metaplasia: the change of one kind of tissue to another, which may be pre-cancerous.[9]

Abbreviations are listed in *Appendix 1*.

Definitions of terms relating to diagnostic test accuracy are provided in *Appendix 2*.

Introduction

GORD is a common chronic condition where acid from the stomach leaks into the oesophagus.[11] Common symptoms include heartburn and an unpleasant taste at the back of the mouth. Chronic reflux can lead to changes in the cells lining the oesophagus and the development of a condition called Barrett's oesophagus. People with chronic reflux and multiple risk factors (aged 50 years or older, white, male, obese) may be referred for an endoscopy to check for Barrett's oesophagus.[4]

The cells lining the oesophagus normally look flat.[3] In people with Barrett's oesophagus, these cells become more like the columnar shaped cells found in the lining of the stomach and bowel. In a small number of people, Barrett's oesophagus can develop into oesophageal cancer over a period of years.[1, 3] People diagnosed with Barrett's oesophagus undergo regular endoscopic surveillance to check that they are not developing cancer.[1, 3]

Oesophageal cancer does not usually cause any symptoms in the early stages when the tumour is small.[12] As a result, the majority of patients present with symptoms of advanced disease and their prognosis is very poor.[1, 12]

Investigative endoscopies in people with chronic reflux and surveillance endoscopies in people with Barrett's oesophagus contribute to a high demand for endoscopy services. because the majority will not have Barrett's oesophagus or cancer. During the COVID-19 pandemic, many endoscopies were cancelled resulting in long patient waiting lists.[5] The Scottish Government recognises the potential for capsule sponge technologies to improve patient access to cancer diagnosis and reduce endoscopy waiting times by providing an alternative to endoscopy for people with chronic reflux or Barrett's oesophagus.[6, 7]

Research question

Are capsule sponge technologies effective and acceptable alternatives to endoscopy for the detection of Barrett's oesophagus and early stage oesophageal cancer?

Literature search

A systematic search of the secondary literature was carried out between 3 and 7 July 2023 to identify systematic reviews, health technology assessments and other evidence based reports. Medline, Medline in process, Embase and CINAHL databases were searched for systematic reviews and meta-analyses.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: gastro-oesophageal reflux, Barrett's oesophagus, oesophageal cancer, Cytosponge™, EndoSign®, sponge on a string and capsule sponge. A full list of resources searched and terms used is available on request.

Health technology description

Capsule sponge devices

We identified four capsule sponge technologies: Cytosponge™, EndoSign®, EsophaCap™ and EsoCheck™.[6, 13, 14] Since there is only one observational study published on the EsophaCap™ and EsoCheck™ devices, and neither device is used in the United Kingdom (UK), these two devices are not considered further.

Cytosponge™ (manufactured by Medtronic) is a single use capsule sponge device that collects cells from the lining of the oesophagus.[15] Cytosponge™ consists of a spherical polyester sponge within a small vegetarian gelatin capsule, that is attached to a string and a piece of card.[6, 15] Patients swallow the capsule and string with a drink of water, while a nurse holds the piece of card.[6] Once swallowed, the gelatin capsule dissolves and the sponge expands in the stomach.[15] After approximately 5 minutes, the rough textured sponge is pulled up from the stomach using the string, collecting cells from the lining of the oesophagus. Sedation is not required for this procedure, but patients may be offered an anaesthetic throat spray to reduce discomfort when removing the sponge.[6]

The EndoSign® capsule sponge (manufactured by Cyted Ltd) consists of an applicator housing a small vegetarian gelatin capsule.[13, 16] The capsule contains a sponge attached to pre-bunched surgical string. The sponge is swallowed, retained in the stomach for approximately 5 minutes, and then

retrieved in a similar manner to the Cytosponge™ device. Patients undergoing an EndoSign® test can also be offered the anaesthetic throat spray.

Cyted Ltd provide the EndoSign® device and a comprehensive biomarker analysis of the cell samples collected.[13, 16] The Cyted laboratories initially provided the same diagnostic analyses of cell samples collected using the Cytosponge™ device as part of an agreement with Medtronic. This arrangement has been discontinued and it is not known who now processes Cytosponge™ samples. Results of the Cyted laboratory analyses are usually available to clinicians within 14 days. Cell preservation kits, packaging and courier collection are all provided by Cyted Ltd and included as part of the EndoSign® service.[16]

Three biomarker tests are applied to cell samples collected using capsule sponge technologies:

- an antibody test to identify TFF3, an indicator of intestinal metaplasia and Barrett's oesophagus
- a test for tumour protein 53 (p53), the most prevalent biomarker of malignant changes in Barrett's cells
- haematoxylin and eosin staining to detect cellular atypia.[15, 17]

Capsule sponge tests are contraindicated in people who:

- have dysphagia or swallowing disorders
- have anatomical abnormalities of the oesophagus or stomach
- have had oesophageal radiofrequency ablation, an oesophageal mucosal resection or an invasive oesophageal or gastric procedure in the past 2 months
- have portal hypertension or oesophageal varices
- are pregnant
- are taking anticoagulants.

Endoscopy

An upper oesophageal endoscopy uses a long, thin, flexible tube with a light and camera at one end (endoscope) to examine the lining of the oesophagus.[11] The procedure is usually carried out in secondary care while the patient is awake, though they may be given a sedative to help them relax if necessary. Biopsies can be taken from the oesophageal lining during an endoscopy.

Use of capsule sponge technologies in Scotland

After an initial pilot using Cytosponge™, NHSScotland changed the capsule device being used after safety concerns were raised by patients.

The EndoSign® device is currently used in two groups of patients in secondary care in NHSScotland:

- to triage patients on a waiting list for Barrett's oesophagus surveillance endoscopy who have had their endoscopy delayed
- as an alternative investigation for patients with chronic reflux symptoms who have been referred to secondary care for an endoscopy, to reduce pressure on endoscopy services from long waiting lists.

A third potential patient population is patients in primary care who have chronic reflux symptoms. In this population the capsule sponge would be used as a screening test for Barrett's oesophagus.

Epidemiology

Chronic reflux

Known risk factors for GORD include hiatus hernias, certain foods, heavy alcohol consumption, smoking and pregnancy.[18] A link between obesity and chronic reflux has also been observed.[18]

The prevalence of chronic reflux varies worldwide. It is estimated to affect between 8.8% and 25.9% of adults in Europe.[19] The prevalence of chronic reflux increases with age and is more common in women. A systematic review of the epidemiology of GORD reported a UK incidence of approximately 5 per 1,000 person-years.[19]

Chronic reflux is a risk factor for developing Barrett's oesophagus and oesophageal cancer.[2] An estimated 5–10% of adults with chronic reflux will develop Barrett's oesophagus.[20]

Barrett's oesophagus

Barrett's oesophagus is more common in men than women and becomes more common with age.[3] Other risk factors include a history of symptomatic reflux, being overweight, a white ethnic background and a family history of Barrett's oesophagus.[3, 21]

Barrett's oesophagus is prevalent in 1.5–2.5% of the adult population in the UK, with around 60,000 new cases per year (annual incidence around 0.1%).[20] Approximately 15–20% of adults undergoing endoscopic investigation of symptomatic reflux receive a diagnosis of Barrett's oesophagus. The condition can also develop without symptoms.

The rate of progression to cancer among patients with Barrett's oesophagus in the UK is approximately 1% per year.[3] An estimated 3% to 13% of people with Barrett's oesophagus in the UK will develop oesophageal adenocarcinoma in their lifetime. The combined incidence of high grade dysplasia and oesophageal adenocarcinoma in patients with Barrett's oesophagus under surveillance in the UK has been estimated at 13.0 per 1,000 patient-years (95 % CI 7.4 to 22.8).[20]

Oesophageal cancer

Approximately two-thirds of newly diagnosed oesophageal cancers in the UK are adenocarcinomas.[22]

Oesophageal cancer is more common in men than women and incidence increases with age.[23] The incidence of oesophageal cancer in the UK is highest in people aged 85–89 years, with around 41 % of new cases being diagnosed in people aged 75 and over. Age standardised incidence of oesophageal cancer in Scotland is higher than the UK average (*Table 1*).[24]

Table 1: Age standardised incidence of oesophageal cancer per 100,000 population in Scotland and the UK as a whole 2016–2018[24]

	Scotland (95% CI)	UK average (95% CI)
Males	25.5 (24.3 to 26.7)	22.7 (22.3 to 23.0)
Females	10.3 (9.6 to 11.0)	8.4 (8.2 to 8.6)
All	17.2 (16.6 to 17.9)	15.0 (14.8 to 15.2)

In 2021, age standardised mortality from any oesophageal cancer was 15.8 per 100,000 person-years at risk (95% CI 14.8 to 17.0) (*Table 2*).[25] The average risk of mortality attributable to oesophageal adenocarcinoma among patients with Barrett's oesophagus under surveillance is estimated as 0.3% per year.[20]

Table 2: Scottish age standardised oesophageal cancer mortality per 100,000 person-years at risk[25]

	Mortality in 2021 (95% CI)
Males	23.1 (21.2 to 25.1)
Females	8.6 (7.6 to 9.7)
All	15.8 (14.8 to 17.0)

The majority of patients diagnosed with oesophageal cancer present with advanced disease.[1] The early detection of oesophageal cancer is associated with improved survival rates. Patients with early stage oesophageal cancer have a 5-year survival rate of approximately 95% compared with 5–40% for patients with advanced disease at diagnosis.[2]

Oesophageal cancer incidence and mortality rates are higher among people from the most deprived category of the Scottish Index of Multiple Deprivation (SIMD) compared with the least deprived group (*Table 3*).[25] This may reflect increased exposure to risk factors, such as smoking, alcohol consumption and obesity, in more deprived areas.[26] In England, 21.2% of patients diagnosed with oesophageal cancer who live in the least deprived areas survive for 5 years or more.[23] The survival rate drops to 13.6% for people who live in the most deprived areas. Oesophageal cancer mortality rates are generally lower in people from non-white ethnic backgrounds compared with people from a white ethnic background in England and Wales.[23]

Table 3: Age standardised oesophageal cancer incidence and mortality per 100,000 person-years at risk by SIMD category[25]

SIMD	Incidence rate 2016–2020 (95% CI)	Mortality rate 2017–2021 (95% CI)
5 (least deprived)	13.2 (12.3 to 14.2)	12.9 (12.0 to 13.9)
4	13.5 (12.5 to 14.5)	13.4 (12.4 to 13.4)
3	17.0 (15.9 to 18.1)	16.6 (15.5 to 17.7)
2	19.2 (18.0 to 20.4)	18.3 (17.1 to 19.5)
1 (most deprived)	20.8 (19.5 to 22.2)	20.1 (18.8 to 21.5)

Clinical effectiveness

All of the clinical effectiveness evidence on capsule sponge technologies relates to the Cytosponge™ device. Since the EndoSign® device is similar in design and function, and the laboratory analysis remains the same, we have assumed that this evidence can be generalised to both devices.

Diagnostic accuracy of capsule sponge technologies

A well conducted systematic review assessed the efficacy of Cytosponge™ plus TFF3 testing, compared with endoscopic biopsy (assumed 100 % accuracy), for the detection of Barrett's oesophagus, dysplasia and cancer.[27] Thirteen diagnostic studies are included in the systematic review (n=3,786): one RCT, three cohort studies, four case-control studies and five cross-sectional studies. Study quality was assessed by the systematic review authors using the National Institute for Health (United States, US) appraisal tools. All studies were rated as good or fair quality, suggesting low to moderate risk of bias. There is no indication of whether the studies were conducted in primary or secondary care. The systematic review authors note that the research team that originally developed the Cytosponge™ device conducted the majority of the studies identified. The review authors were not involved in the development of Cytosponge™.

Patients with chronic reflux

There are six studies (n=1,957) in the systematic review that report the sensitivity and specificity of capsule sponge devices for the detection of Barrett's oesophagus (*Table 4*). One additional study reports sensitivity only.[28] Based on the six studies, pooled sensitivity and specificity in this population are 81% and 91%, respectively. In other words, 19% of patients tested for Barrett's oesophagus using a capsule sponge device would receive a false negative result and 9% a false positive result. There is variability in the sensitivity estimates reported in studies that evaluated the Cytosponge™ device: median sensitivity 78.0%, range 71.4% to 90.9%. Sensitivity improves when longer Barrett's oesophagus segments are present.[2]

Table 4: Diagnostic accuracy of capsule sponge devices for the detection of Barrett's oesophagus in patients with chronic reflux[27]

Study	Patients	Sensitivity	Specificity	Adverse events
Iyer et al (2016)[29] RCT (US)	Esophacap™ device n=41 (40 swallowed) 21 patients with BO (cases); 20 patients without BO (controls) Median age: 66 years (cases), 61 years (controls)	100%	100%	No adverse events reported
Kadri et al (2010)[30] Cohort study (UK)	Cytosponge™ device n=504 (501 swallowed) Patients with chronic reflux Median age: 62 years (range 56 to 66)	73.3% (patches ≥1cm) 90.0% (patches ≥2cm)	93.8% (patches ≥1cm) 93.5% (patches ≥2cm)	No serious adverse events reported
Ross-Innes et al (2015)[31] Case-control (UK) [BEST2]	Cytosponge™ device n=1,110 (1,042 swallowed) 463 patients with dyspepsia (controls); 647 patients with BO (cases) Median age: 66 years (cases), 56 years (controls)	79.9%	92.4%	No serious adverse events 16.7% had bleeding from oesophageal abrasions
Katz-Summercom et al (2017)[32] Case-control (UK)	Cytosponge™ device n=59 Patients with known BO (28 with dysplasia, 31 with no dysplasia) Median age: 66.5 years (dysplasia), 64 years (no dysplasia)	71.4%	90.3%	Not reported
Lao-Sineix et al (2009)[33] Case-control (UK)	Cytosponge™ device n=146 Patients scheduled for endoscopy 47 cases, 99 healthy controls	78%	94%	Not reported
Lao-Sineix et al (2007)[34] Case-control (UK)	Unknown sponge type n=97 43 cases, 54 healthy controls	67.5% 76% (patches >3 cm)	67.3%	Not reported
Lao-Sineix et al (2015)[28] Cross-sectional (UK)	Cytosponge™ device n=73 (72 swallowed) Patients with known BO	91.5%	Not reported	95% had oesophageal abrasions
Pooled accuracy*	**n=1,957**	**81%**	**91%**	

*Only the six studies from the table that report both sensitivity and specificity were included in the pooled estimate

BO = Barrett's oesophagus

Patients with Barrett's oesophagus under surveillance

A cross-sectional study (n=891) assessed the diagnostic accuracy of Cytosponge™ combined with biomarker testing and clinical risk factors for detecting dysplasia and oesophageal cancer in patients with confirmed Barrett's oesophagus under surveillance.[35] The authors of the study developed the Cytosponge™ technology. Two groups of patients were derived from the BEST2 and BEST3 trial participants; a training cohort of 557 patients and a validation cohort of 334 patients. The biomarkers assessed were p53 overexpression and atypia. The clinical risk factors examined were patient age, sex and the maximum dimensions of Barrett's oesophagus segments. Three potential diagnostic models were developed using the training cohort and tested in the validation cohort: Cytosponge™ biomarker positive only, Cytosponge™ biomarker positive plus clinical risk factors and clinical risk factors only (*Table 5*).

Study participants were mostly male; 81% in the training cohort and 75% in the validation cohort. Median age of participants was 65 years in the training cohort and 67 years in the validation cohort. Endoscopic biopsies (the reference standard) found high grade dysplasia or oesophageal cancer in 17% of patients in the training cohort and 10% of patients in the validation cohort. Based on Cytosponge™ testing, 24% of patients in the training cohort and 23% of patients in the validation cohort had cellular atypia, p53 overexpression or both.

In the Cytosponge™ biomarker positive model, sensitivity and specificity for high grade dysplasia or cancer in the validation cohort were 89% and 84%, respectively (*Table 5*). This means that using Cytosponge™ with biomarker testing, 11% of patients would receive a false negative result and 16% would receive a false positive result. Sensitivity and specificity were not substantially improved when clinical risk factors were added to the model.

Table 5: Diagnostic accuracy of three models for diagnosing dysplasia and oesophageal cancer in patients with Barrett's oesophagus under routine surveillance[35]

	High grade dysplasia or cancer		Any grade dysplasia or cancer	
	Training cohort	Validation cohort	Training cohort	Validation cohort
Cytosponge™ biomarker positive only				
Sensitivity (95% CI)	0.74 (0.65 to 0.83)	0.89 (0.77 to 0.97)	0.65 (0.57 to 0.72)	0.72 (0.61 to 0.83)
Specificity (95% CI)	0.86 (0.83 to 0.89)	0.84 (0.80 to 0.88)	0.89 (0.87 to 0.92)	0.88 (0.84 to 0.91)
Cytosponge™ biomarker positive plus clinical risk factors				
Sensitivity (95% CI)	0.77 (0.68 to 0.86)	0.80 (0.66 to 0.91)	0.70 (0.63 to 0.78)	0.69 (0.56 to 0.80)
Specificity (95% CI)	0.86 (0.82 to 0.89)	0.87 (0.83 to 0.91)	0.86 (0.82 to 0.89)	0.91 (0.88 to 0.94)
Clinical risk factors only				
Sensitivity (95% CI)	0.66 (0.57 to 0.76)	0.91 (0.80 to 1.00)	0.62 (0.53 to 0.69)	0.80 (0.69 to 0.89)
Specificity (95% CI)	0.65 (0.60 to 0.69)	0.46 (0.40 to 0.51)	0.65 (0.61 to 0.70)	0.50 (0.44 to 0.56)

Rate of diagnosis of Barrett's oesophagus in patients with chronic reflux (primary care screening population)

An RCT, conducted by the team that developed Cytosponge™, compared Cytosponge™ plus TFF3 testing with usual care for the diagnosis of Barrett's oesophagus in primary care patients with chronic reflux.[36] The RCT involved patients from 109 general practices in England. Study participants had recurrent symptoms of GORD, were aged 50 or older, and had been taking acid suppressant medications for at least 6 months in the past year. People with a confirmed diagnosis of Barrett's oesophagus or an endoscopy in the previous 5 years were excluded. Patients were followed up for a weighted average of 12 months (range 8 to 18 months).

The intervention group were offered a Cytosponge™ test with a subsequent endoscopy if they had a positive result. Making the Cytosponge™ test optional in the intervention group could have introduced selection bias to the study, because patients who agreed to have the test may have had more problematic symptoms than those who declined. The control group received usual care from their GP, including an endoscopy referral if appropriate.

All patients were included in an intention to treat analysis, including the majority of patients in the intervention group who did not receive a Cytosponge™ test. It is unclear what effect this had on the study findings.

In total 13,514 patients were enrolled in the trial. Median age of participants was 69 years [inter-quartile range (IQR) 61 to 74]. In the intervention group 4,155/6,983 (59.5 %) patients did not reply to the offer of a Cytosponge™ test or declined the test. A further 346 patients did not book or attend an appointment for their test. Of the 2,096 patients eligible for Cytosponge™ testing, 1,750 attended their appointment and 1,654 successfully swallowed the capsule sponge (24% of patients randomised to the intervention group).

Nineteen percent (311/1,654) of patients who successfully swallowed the Cytosponge™ had a low confidence negative or equivocal result. One hundred and fifty patients still had a low confidence result after a second Cytosponge™ test. Of the group of patients who successfully swallowed the Cytosponge™, 221 (13%) tested positive for TFF3 and had a follow-up endoscopy. Ten people with a positive test declined a follow-up endoscopy. Of those patients who had a follow-up endoscopy, 127 (57%) had their Barrett's oesophagus diagnosis confirmed and four (2%) were diagnosed with early oesophageal cancer. Ninety patients did not have Barrett's oesophagus on their follow-up endoscopy; 33 were found to have intestinal metaplasia – a pre-cancerous change in oesophageal tissues.

In the intention to treat analysis the rate of Barrett's oesophagus diagnosis per 1,000 person-years was two in the usual care group and 20.2 in the intervention group. The absolute difference in rate of Barrett's oesophagus diagnosis was 18.3 per 1,000 person-years (95% CI 14.8 to 21.8). The adjusted risk ratio for Barrett's oesophagus diagnosis was 10.6 per 1,000 patient-years (95% CI 6.0 to 18.8, $p<0.0001$) indicating a far higher rate of diagnosis in the Cytosponge™ group compared with usual care. A limitation of the analysis is that it is unknown how many patients in the usual care group had an endoscopy to diagnose Barrett's oesophagus or oesophageal cancer during the study period.

Nine patients in the intervention group were diagnosed with dysplastic Barrett's oesophagus (n=4) or early stage oesophagogastric cancer (n=5). No participants in the control group were diagnosed with dysplastic Barrett's oesophagus or early stage oesophagogastric cancer.

Patient triage for endoscopy

Patients with chronic reflux referred for an endoscopy

A retrospective cohort study examined 2 years of Cytosponge™ samples analysed at the Cyted laboratory.[17] The authors of the study were involved in developing the Cytosponge™ technology, founded Cyted Ltd or were employed by Cyted Ltd.

In total, 10,577 Cytosponge™ samples collected at 61 hospitals across Scotland and England were analysed by the Cyted laboratory during the study period. The samples were from two patient populations; 42.1% (4,456/10,577) were from patients with chronic reflux who were referred for an endoscopy and 57.9% (6,121/10,577) were from patients with Barrett's oesophagus under routine surveillance. A sufficient sample of oesophageal cells was obtained from the Cytosponge™ in 92.5% of patients (9,784 patients); 43.9% of successful samples were from Scottish patients.

In the chronic reflux population, 55.1% of patients tested were women and 18.3% were aged 70 years or older. The Cytosponge™ samples were TFF3 positive for 13.6% of patients tested. Of these TFF3 positive samples, 5.2% had cellular atypia, p53 overexpression or both. TFF3 positivity and atypia were significantly more common in samples from Scottish patients compared with samples from English patients (17.0% versus 12.3%, p<0.001 and 2.4% versus 1.2%, p=0.012, respectively).

Patients with chronic reflux who had a positive result for atypia, p53 or both, were considered high risk for Barrett's oesophagus or oesophageal cancer and referred for an urgent endoscopy (1.6%). Patients who had a positive TFF3 test but were negative for atypia and p53, were referred for routine endoscopy (12.9%). Patients who tested negative for TFF3, atypia and p53 were managed according to their ongoing symptoms (85.6%) and did not receive an endoscopy.

Patients with Barrett's oesophagus under surveillance

The study described in the section above found that the majority of patients with Barrett's oesophagus under routine surveillance were males (70.5%) over the age of 60 years (70.4%).[17] The proportion of TFF3 positive Cytosponge™ tests was greater in this patient population (63.4%). In total, 7.6% of patients had cellular atypia suggestive of inflammation or cancer. And 2.1% had suspected high grade dysplasia or early oesophageal cancer. The proportion of patients testing positive for atypia or p53 overexpression increased with increasing length of Barrett's oesophagus segments [odds ratio (OR) 1.08 per cm, 95% CI 1.05 to 1.10, p<0.001 and OR 1.07 per cm, 95% CI 1.04 to 1.09, p<0.001, respectively].

In total, 8.7% of patients were considered high risk and referred for an urgent endoscopy. Twenty-nine percent of patients were considered moderate risk and referred for a routine endoscopy. Approximately two-thirds (62.6%) of patients were considered low risk and may not meet the criteria for a Barrett's oesophagus diagnosis.

The cross-sectional study that reported on the diagnostic accuracy of Cytosponge™ testing plus biomarkers or clinical risk factors in patients with Barrett's oesophagus, also described triaging these patients for endoscopy.[35] This element of the study involved three patient cohorts: patients from the training and validation cohorts in *Table 5* and a prospective cohort (n=223) of patients derived from participants in the DELTA trial. Patients were triaged into high risk (Cytosponge™ biomarker positive), moderate risk (clinical risk factors) and low risk (no biomarkers or clinical risk factors) for oesophageal cancer based on their Cytosponge™ result.

The risk of high grade dysplasia or cancer in the Cytosponge™ biomarker positive (high risk) group was 52% (68/132 patients) in the training cohort and 41% in the validation cohort (31/75). In the low risk group, the risk of high grade dysplasia or cancer was 2% (7/395) across the training and validation cohorts.

Diagnosis of high grade dysplasia or cancer at endoscopy was three times higher in patients with a positive Cytosponge™ biomarker test compared with endoscopic surveillance alone (47% versus 14%). The triage process resulted in 17% of patients (n=39) in the prospective cohort being urgently referred for an endoscopy based on a high risk of oesophageal cancer. Seventeen percent of patients were triaged to a moderate risk group and 65% were considered low risk. The study authors proposed that low risk patients undergo repeat surveillance using Cytosponge™ rather than endoscopy. Moderate risk patients could receive either more frequent surveillance using Cytosponge™ or alternate between Cytosponge™ and endoscopy surveillance.

NHS data analysis

The data in this section describes the observed effects of implementing capsule sponge testing in the NHS. These data have been gathered by clinicians and researchers working in NHSScotland or NHS England. The data have not been derived from published studies or subjected to peer review.

Evaluation of primary data from NHSScotland

The ANIA Collaborative asked us to evaluate the use of Cytosponge™ testing in NHSScotland. We analysed data collected across 11 health boards for patients with chronic reflux who had been referred for an endoscopy and patients with Barrett's oesophagus under routine surveillance.

A clinical researcher who worked with the Cytosponge™ pilot team entered data into a pre-prepared Microsoft Excel workbook. The data covered the period from 14 September 2020 to 30 April 2023. We used R© software (version 4.2.2) to analyse the data.

For patients with chronic reflux, Cytosponge™ testing is intended to reduce the number of follow-up endoscopies needed, resulting in resource and cost savings. For patients with Barrett's oesophagus under surveillance, Cytosponge™ testing is intended to speed up time to diagnosis and treatment through its use as a triaging tool.

Patients with chronic reflux

Since we do not have comparator data, we are unable to comment on whether Cytosponge™ results in a reduction in the number of follow-up endoscopies needed. We will describe the use of Cytosponge™ within the clinical pathway instead.

One thousand three hundred and five patients with chronic reflux were included in dataset. The average age of the patients was 55 years. The majority of patients (58.2%) were women (*Appendix 3, Table A*).

Most Cytosponge™ procedures collected enough cells for testing and were described as successful (89.75%). Of the successful Cytosponge™ tests, about 10% were positive and a follow-up endoscopy was requested for the patient (*Table 6*).

Around 10% of tests were categorised as failures because the Cytosponge™ did not collect enough cells for testing. A small proportion of tests (5.78%) needed to be repeated.

Approximately one fifth of all patients tested (22%) had a follow-up endoscopy. Most patients with chronic reflux who had a follow-up endoscopy were not diagnosed with a serious condition (*Table 6*). Fifteen percent of patients were diagnosed with Barrett's oesophagus. Less than 1% of patients were diagnosed with dysplasia or cancer.

Table 6: Overview capsule sponge test outcomes for patients with chronic reflux (n=1,305)

Outcome	n	Percentage (%)
Procedure outcomes		
n Cytosponge™ procedures	1,385	–
n Cytosponge™ procedures that collected enough cells for testing	1,243	–
Success rate	–	89.75
n Cytosponge™ procedures that did not collect enough cells for testing	142	–
Failure rate	-	10.25
n repeat Cytosponge™ procedures	80	5.78
n positive Cytosponge™ tests	140	10.11
n follow-up endoscopies	305	22.02
n people who do not have a follow-up endoscopy	1,000	72.20
Test outcomes		
Barrett's oesophagus	46	15.08
Low grade dysplasia	1	0.33
High grade dysplasia	0	0.00
Oesophageal adenocarcinoma	0	0.00
Gastric adenocarcinoma	3	0.98
Gastric lymphoma	1	0.33
Neuroendocrine carcinoma	1	0.33
No serious pathology	253	82.95

Number of follow-up endoscopies includes the number of Cytosponge™ procedures that did not collect enough cells for sampling (n=142), number of positive Cytosponge™ tests (n=140) and 23 Cytosponge™ tests that were ordered by a clinician for ongoing symptoms.

Prior to introducing Cytosponge™ in NHSScotland, all patients with concerning chronic reflux symptoms would have been referred to secondary care for an endoscopy (Professor G Fullarton, Consultant Surgeon and Associate Professor of Surgery, NHS Greater Glasgow and Clyde. Personal communication, 16 November 2023). In our analysis, 22% of patients with chronic reflux had a follow-up endoscopy, suggesting that a 78% decrease in demand for endoscopies in this patient group may be achievable.

There are important caveats to the interpretation and scope of the decrease in endoscopies needed for patients with chronic reflux. In practice, clinicians use their judgement and consider patient preferences when deciding whether to refer someone for an endoscopy. The decrease in endoscopies may also be smaller than expected because additional tests may be ordered by clinicians, for example, referring patients for an endoscopy despite a negative Cytosponge™ test.

We do not have data on the real world diagnostic accuracy of Cytosponge™ in our evaluation population.

Patients with Barrett's oesophagus under surveillance

Since we do not have comparator data (for example, endoscopy follow-up), we cannot comment on whether Cytosponge™ testing results in speedier diagnosis and treatment compared with endoscopy. We will describe the use of Cytosponge™ within each stage of the clinical pathway instead.

There were 3,745 patients with Barrett's oesophagus under surveillance in the dataset, with an average age of 64 years. Most patients (67.64%) were male (*Appendix 3, Table B*). A subgroup of 299 patients were described as high risk. Most high risk patients (n=223) were male with an average age of 68 years.

Most Cytosponge™ procedures (89.15%) collected enough cells for testing. Approximately 11% of Cytosponge™ tests were repeated to collect more cells (insufficient sampling, 49.02%) or because they were requested by a clinician (50.98%, *Table 7*).

Most patients (n=563) who had a follow-up endoscopy did not have a serious condition (*Table 7*). The majority of these patients (71.23%) were given a diagnosis of intestinal metaplasia. Less than 2% of patients were diagnosed with low grade dysplasia. Less than 1% of patients were diagnosed with high grade dysplasia or cancer.

Prior to introducing Cytosponge™, all patients who are under surveillance for their Barrett's oesophagus would have received routine endoscopies as per UK guidelines.[37] In our evaluation, 23% of patients under surveillance received a follow-up endoscopy, suggesting a 77% decrease in demand for endoscopies in this patient group. The decrease in endoscopies may be smaller than

expected because additional tests may be ordered by clinicians, for example, referring patients for a surveillance endoscopy despite a negative Cytosponge™ test.

Table 7: Overview of outcomes for patients with Barrett's oesophagus under surveillance (n=3,745)

Outcome	n	Percentage (%)
Procedure outcomes		
n Cytosponge™ procedures	4,204	–
n high risk patients	299	7.98
n Cytosponge™ procedures that did not collect enough cells for testing	456	–
Failure rate	–	10.85
n Cytosponge™ procedures that collected enough cells for testing	3,748	–
Success rate	–	89.15
n repeat Cytosponge™ procedures	459	10.92
Previously insufficient samples	225	49.02
Clinically indicated	234	50.98
Test outcomes		
Low grade dysplasia	58	1.55
Indefinite	34	58.62
High grade dysplasia	26	0.69
Oesophageal adenocarcinoma	25	0.67
Oesophageal squamous cell carcinoma	2	0.05
No serious pathology	563	15.03
No biopsies	25	4.44
No intestinal metaplasia	137	24.33
Intestinal metaplasia	401	71.23

Total number of follow-up endoscopies = 973 (calculated from diagnostic categories in primary outcomes). Total number of Cytosponge™ procedures includes patients where the procedure collected enough cells for sampling (n=3,748) and repeat procedures (n=459). Three patients had a successful procedure but had a second test for clinical reasons. These patients are not counted twice in the total number (n=4,204).

On average, high risk patients (n=299) had a Cytosponge™ procedure 1,187 days (approximately 39 months) after their last routine surveillance endoscopy. They started treatment an average of 1,538 days (approximately 51 months) after their last routine surveillance endoscopy.

Patients with urgent endoscopy referrals, triggered by a Cytosponge™ result (n=281), received an endoscopy after an average of 87 days (approximately 3 months) and a diagnosis after 111 days (approximately 4 months). Patients received treatment after an average of 244 days (approximately 8 months, *Appendix 3, Table C*).

No data were available on the number of days from last endoscopy to cytology diagnosis.

CytoScot analysis of data from NHSScotland: patients with Barrett's oesophagus under surveillance

An unpublished retrospective cohort study analysed NHSScotland data on the use of Cytosponge™ to triage patients with Barrett's oesophagus under routine surveillance.[38] The study was conducted by the CytoScot group responsible for piloting capsule sponge testing in Scotland. It has not been peer reviewed or published. The pilot was conducted during the COVID-19 pandemic when many endoscopic surveillance appointments were cancelled. The patients described in this study are a subset of those in our evaluation of data from NHSScotland.

The study analysed 2 years of data (September 2020 to September 2022) from 11 Scottish health boards. Delays to surveillance testing were defined as the recommended surveillance interval (in months) subtracted from the interval between the patient's last surveillance endoscopy and their Cytosponge™ test. If the difference was greater than 3 months, the patient was classed as having their surveillance test delayed.

A total of 3,223 Cytosponge™ tests in patients with Barrett's oesophagus under routine surveillance were recorded during the study period (1,478 tests in year one and 1,745 tests in year two). Sixty-eight percent of patients were male. Median patient age was 67 years (IQR 59 to 73) in the first year of the study.

Introducing Cytosponge™ testing led to significant reductions in the length of delays in surveillance and the proportion of patients experiencing long delays. The median length of surveillance delay was reduced from 9 months in year one to 5 months in year two, $p<0.001$. The proportion of patients who experienced surveillance delays of more than 3 months decreased from 72.5% to 57.0%, $p<0.001$.

Four hundred and twenty-five patients (13.2%) had a follow-up endoscopy after their Cytosponge™ test. More than half of these endoscopies (57.9%) were in response to positive findings on the capsule sponge test.

Within the group of patients identified as high risk (atypia, p53 positive or both, n=271, 8.4%) the median time from a Cytosponge™ test to follow-up endoscopy was 2 months (IQR 1 to 3 months). In total, 90.8% (n=246) of high risk patients received an urgent endoscopy within 12 months of their Cytosponge™ test.

Ten out of 18 patients in the high risk group (55.5%) had dysplasia on endoscopic biopsy when surveillance appointments were delayed by more than 24 months. A total of 43 patients were diagnosed with dysplasia or cancer on endoscopic biopsy, 74.4% of them had delayed surveillance.

Limitations to this study include variations in the definition of a normal surveillance interval between health boards and a lack of comparator data from endoscopy.

Cytosponge™ in NHS England: patients with chronic reflux referred for endoscopy

A pilot project in NHS England introduced Cytosponge™ as a triage tool for patients with low risk reflux symptoms who were referred for an endoscopy.[39] Mixed methods data were gathered from 17 cancer alliances and 30 hospital sites across England for all relevant patients seen between February 2021 and March 2022. Quantitative data were obtained from clinical data systems (n=1,549) and patient surveys (n=352). Qualitative data were gathered from interviews with clinical staff (n=22) and patients (n=28).

Ninety-three percent of patients offered a Cytosponge™ test accepted. Approximately one in five patients (19%) did not complete the procedure after accepting the initial invite. The majority of patients (94.8%) who attended their appointment successfully completed the Cytosponge™ test and were able to swallow the sponge on the first attempt (86.9%).

In total, 78% of patients who completed the Cytosponge™ test were removed from the endoscopy waiting list (*Table 8*). The proportion of patients referred for an endoscopy after their Cytosponge™ test was reduced by 20% (from 27.9% of patients to 8.1%) within the 1 year pilot.

Barrett's oesophagus was diagnosed in 27.1% of patients with a positive Cytosponge™ test and 3.5% of patients with an inconclusive test result. One in four endoscopy referrals in patients with a positive Cytosponge™ test were urgent compared with one in seven for patients with equivocal or negative results. The observed prevalence of Barrett's oesophagus across all capsule sponge tests was 1.8%. This rose to 11.2% among patients referred for a follow-up endoscopy.

Table 8: Overview of outcomes for patients with chronic reflux tested with Cytosponge™ in NHS England[39]

	All test results n (%)	Positive results n (%)	Unclear test results n (%)	Negative test results n (%)	Unknown
Completed Cytosponge™	**1,411**	**129**	**128**	**1,060**	**94**
Discharged	734 (52.0)	8 (6.2)	2 (1.56)	711 (67.1)	13 (13.8)
Urgent endoscopy	46 (3.3)	23 (17.8)	11 (8.6)	10 (0.9)	2 (2.1)
Routine endoscopy	220 (15.6)	77 (59.7)	64 (50.0)	62 (5.85)	17 (18.1)
Unknown urgency endoscopy	41 (2.9)	11 (8.5)	12 (9.4)	7 (0.7)	11 (11.7)
Retest	30 (2.1)	5 (3.9)	20 (15.6)	4 (0.4)	1 (1.1)
Other	176 (12.5)	2 (1.6)	13 (10.2)	147 (13.9)	–
Missing	164 (11.6)	3 (2.3)	6 (4.7))	119 (11.2)	50 (53.2)
Completed endoscopy*	**223 (73.0 %)**	**81 (73.0 %)**	**57 (65.5 %)**	**64 (81.0 %)**	–
Barrett's oesophagus	25 (11.2)	22 (27.2)	2 (3.5)	0	–
Oesophageal cancer	0	0	0	0	–
Inflammation	19 (8.5)	7 (8.6)	3 (5.3)	9 (14.1)	–
Intestinal metaplasia	8 (4.0)	7 (8.6)	1 (1.8)	0	–
Ulcer	3 (1.4)	1 (1.2)	1 (1.8)	1 (1.6)	–
Oesophagitis	12 (5.4)	6 (7.4)	4 (7.0)	2 (3.1)	–
Hiatus hernia	19 (13.0)	10 (12.4)	8 (14.0)	11 (17.2)	–
Other	10 (4.5)	0	5 (8.8)	2 (3.1)	–

*Percentage of those who were referred for an endoscopy

Most patients (82%) expressed satisfaction with their experience of the Cytosponge™ test. Patients felt that the test:

- was less invasive than an endoscopy
- gave them peace of mind
- involved fewer staff
- could be performed in a less clinical setting (endoscopies are often done in an operating theatre), and
- gave them faster access to appointments and test results.

Patients were less satisfied with their Cytosponge™ test when they felt their original issue had not been resolved, had problems completing the test or had a poor understanding of the test results.

Overall, 94% of patients reported experiencing mild or no pain during or after their Cytosponge™ test. Two-thirds of patients (66%) reported experiencing discomfort during or after the test, with 22% experiencing severe discomfort. Patients did not seem concerned about the level of discomfort felt.

Patients reported experiencing bleeding (3%), a mild throat irritation (64%) and severe or very severe throat irritation (12%). Other side effects included soreness in the chest, difficulties swallowing, a burning sensation, stomach pain, a dry throat, vomiting and strong gag reactions.

Ongoing studies

We identified three relevant ongoing studies (*Table 9*). All three studies are assessing the Cytosponge™ device.

Table 9: Ongoing studies using the Cytosponge™ device

Trial ID	Study title and description	Completion date
NCT04192695	Oesophageal squamous cell cancer surveillance with Cytosponge™ A single arm study to identify novel biomarkers associated with oesophageal squamous cell carcinoma	November 2024
NCT03366012	Rapid assessment of oesophageal adenocarcinoma risk test (REACT) A single arm study evaluating the use of Cytosponge™ as a screening test for Barrett's oesophagus in patients with GORD	December 2024
NIHR135565	BEST4: a platform trial to determine whether Cytosponge™ biomarker technology reduces mortality from oesophageal cancer Two related studies: 1) A targeted screening study to determine the extent to which Cytosponge™ testing can reduce the number of people dying from oesophageal cancer 2) A surveillance study looking at whether Cytosponge™ can be used to determine whether a person is at low or high risk of developing oesophageal cancer	October 2035

Safety

The BEST3 trial described above reported adverse events experienced by trial participants.[36] Of 1,654 patients with chronic reflux who successfully completed a Cytosponge™ test, 142 (9%) reported an adverse event. Sixty-three participants (4%) had a sore throat requiring medication or causing problems with eating. One serious adverse event associated with Cytosponge™ testing was reported when a sponge detached from the string and required endoscopic retrieval. Other adverse events included gastrointestinal adverse events, such as indigestion or reflux (19%) and oesophageal or gastric pain (15%).[22]

Data from five studies were combined in a retrospective analysis of prospectively collected data to assess the safety and acceptability of Cytosponge™-TFF3 testing.[40] Participants in the five studies had GORD, Barrett's oesophagus or eosinophilic oesophagitis. Three studies recruited patients with chronic reflux who were referred to secondary care for an endoscopy. One study was in a primary care population with reflux symptoms. One study involved patients with Barrett's oesophagus under routine surveillance. Safety data on the number of attempts to swallow the Cytosponge™, failure to swallow the sponge, serious adverse events and abrasion grade, were collated from the five studies.

The majority of participants in the five studies had GORD (n=1,329, 56.7%) or Barrett's oesophagus (n=987, 40.8%). Median age of participants was 62 years (IQR 54 to 68). Of 2,418 patients across the five studies, 84 (3.5%) were unable to swallow the Cytosponge™ and 50 were withdrawn from the study by their clinician.

Failure to swallow the Cytosponge™ was more than twice as common in patients with Barret's oesophagus (5.7%) compared with patients who had GORD (2.1%). Patients in secondary care were statistically significantly more likely to fail to swallow the Cytosponge™ compared with patients in primary care: OR 5.13, 95 % CI 1.48 to 17.79, p<0.01.

A total of 12 serious adverse events were recorded in the five studies. Only two of these events were deemed to be related to the Cytosponge™ device. In one patient the sponge detached from the string and in another there was bleeding after the sponge was withdrawn.

In 1,075 participants who underwent a Cytosponge™ tests followed by an endoscopy, 85.5% (919/1,075) recorded no or mild abrasions (grade 0–2) on endoscopy. No patient had a grade 5 abrasion requiring endoscopic or surgical intervention.

Field safety notice for Cytosponge™

In June 2023, the MHRA issued an urgent field safety notice for the Medtronic Cytosponge™ device.[41] The notice announced the immediate recall of 15 batches of Cytosponge™ devices. The devices within these batches had an increased risk of the sponge detaching from the string as it was withdrawn from the patient's oesophagus. This could result in device fragments being retained in the

patient's oesophagus or stomach, obstruction of the oesophagus, airway obstruction, a secondary intervention to retrieve the device or aspiration of the device.

Between December 2022 and June 2023, 13 patients worldwide reported the Cytosponge™ device became detached from the string during their procedure. Five of these events were reported by patients in Scotland; two by patients with chronic reflux and three by patients with Barrett's oesophagus under surveillance. All patients underwent an urgent unplanned upper endoscopy to retrieve the sponge from the stomach or oesophagus without further adverse consequences.

Patient and social aspects

Patient experiences of capsule sponge technologies

Two studies explored the experiences of patients with chronic reflux who had a capsule sponge test.[21, 22]

A mixed methods study, nested within the BEST3 trial, explored the experiences of primary care patients with GORD who had a Cytosponge™ test.[21] Participants completed the Spielberger State Trait Anxiety Inventory (STAI-6) at baseline and 1–2 weeks later. Participants who had successfully swallowed the Cytosponge™ device completed an adapted version of the Inventory to Assess Patient Satisfaction (IAPS) questionnaire at 2 weeks follow up. A small purposive sample of patients were interviewed face to face to explore their experiences in more depth. Interviews were conducted within 6 weeks of the Cytosponge™ test and lasted an average of 23 minutes (range 13 to 50 minutes).

In total, 1,750 patients completed the baseline questionnaires and 1,488 participants (90% of successful tests) completed the follow-up questionnaires. Seventy-five patients were invited for an interview and 30 (40%) accepted. Study participants were aged 50 to 99 years of age and 47% were male.

Overall, participants were satisfied with their experience of the Cytosponge™ test and 80% would be willing to have the test again. Patients preferred having the test in a primary care setting and appreciated having a range of appointment options. The lowest levels of patient satisfaction were reported for retrieval of the Cytosponge™.

There was a statistically significant reduction in STAI-6 scores between baseline and follow up ($p<0.001$). An STAI-6 score of 40 was considered the threshold for clinically significant anxiety. At baseline, 24% of participants reported scores of 40 or higher. This reduced to 12% of participants at follow up. Participants described feeling anxious about being able to complete the test or about the test itself. For some participants, their anxiety resolved after they received their test result.

Some interview participants described having difficulty swallowing the sponge because the string was uncomfortable or it was difficult to drink enough water to swallow the sponge and string. These difficulties were not perceived as worrisome. Interviewees who described difficulty with swallowing the capsule and string (gagging, retching or heaving) felt this was because they could not place the capsule far enough back in their throat without triggering their gag reflex.

The second study explored patient and procedure related factors that led to patients having a poor experience of Cytosponge™ testing.[22] Data in this study were also from participants in the BEST3 trial who completed the IAPS and the STAI-6 questionnaires at baseline and 1–2 weeks later. Trial participants who successfully swallowed the Cytosponge™ and completed 15 or more questions on the IAPS questionnaire were included in the study (n=1,458). Individuals who did not successfully swallow the Cytosponge™ (n=96) were excluded.

The majority of patients reported a positive experience with a median overall IAPS score of 1.7 (IQR 1.5 to 2.1) on a scale of one to five, where higher scores indicate a worse experience. The median score in the poor experience group was 2.5 (IQR 2.4 to 2.6). Only 4.7% of participants scored above 2.5 (the preset cut-off for the least positive experience) and 0.5% scored above three.

In multivariable regression analysis, participants who had high or very high anxiety levels were more likely to have a poor experience compared with participants with normal anxiety (OR 2.82, 95% CI 1.92 to 4.13 and OR 4.50, 95% CI 2.71 to 7.48, respectively). Being unable to swallow the Cytosponge™ on the first attempt was significantly associated with a poor experience (OR 3.45, 95% CI 2.21 to 5.38). The odds of having a poor experience were greater for individuals who drank alcohol on most days compared with individuals who never drank alcohol (OR 1.82, 95% CI 1.08 to 3.08). Men were less likely to have a poor experience compared with women (OR 0.56, 95% CI 0.33 to 0.96).

In univariable regression analysis, being male was a predictor of failing to swallow the Cytosponge™ on the first attempt (OR 0.64, 95% CI 0.45 to 0.92). No variables were statistically significant predictors of the failure to swallow in multivariable analysis.

Patient acceptability of capsule sponge technologies

The retrospective analysis of data from five studies described in the safety section, assessed patient acceptability of Cytosponge™ testing.[40] Acceptability data for Cytosponge™ and follow-up endoscopies in patients with a positive test were prospectively gathered using a visual analogue scale (VAS) of 0 to 10. Higher scores indicated greater acceptability.

A total of 2,289 patients completed the VAS, including 1,221 (53.3%) who had a follow-up endoscopy (402 without sedation, 773 with sedation). Overall the Cytosponge™ test was rated as satisfactory, with a median VAS score of 6.0 (IQR 5.0 to 8.0).

Median VAS scores indicated that Cytosponge™ was more acceptable to patients than endoscopy without sedation, but less acceptable than endoscopy with sedation. The Cytosponge™ median VAS score was 6.0 (IQR 5.0 to 8.0) compared with endoscopy without sedation 5.0 (IQR 3.0 to 7.0) and endoscopy with sedation 8.0 (IQR 5.0 to 9.0), p<0.001 for each comparison.

Cytosponge™ had a higher median VAS score among men compared with women: 7.0 (IQR 5.0 to 8.0) versus 6.0 (IQR 5.0 to 8.0), p=0.003. Patients receiving their test in primary care (n=513) had a higher median VAS score compared with patients tested in secondary care (n=1,776): 7.0 (IQR 5.0 to 8.0) versus 6.0 (IQR 5.0 to 8.0), p<0.001.

Public perceptions of capsule sponge technologies

A qualitative analysis explored the acceptability of the Cytosponge™ test in a sample of people from the UK who were living with GORD.[42] Study participants were recruited through an advertisement from a recruitment company email, which may have introduced bias into the study.

A total of 33 people participated in the study; 17 men and 16 women (the total number of people approached is unknown). Median age of participants was 57 years (range 50 to 69) and 45% had experience of having an endoscopy. None of the study participants had experience with Cytosponge™. Ten people were interviewed and 23 people participated in one of four focus groups.

Anticipated physical experiences of Cytosponge™ included concerns about swallowing and extracting the Cytosponge™. For example, participants expressed concerns about swallowing the string, the possibility of the Cytosponge™ getting stuck and gagging or vomiting while trying to swallow the sponge.

Study participants differed in their preferences for what information they would like to receive before having a Cytosponge™ test and the format it should take. There was discussion about whether or not, as patients, they would want be told in advance that a positive Cytosponge™ test would result in further testing, likely an endoscopy.

Participants, particularly those with experience of an endoscopy, felt that Cytosponge™ was preferable physically, practically and economically. Participants were enthusiastic about having the test at their local general practice, not needing an anaesthetic and being able to return to everyday activities immediately.

A cross-sectional study analysed comments posted in response to a video demonstrating the Cytosponge™ test that was loaded onto Facebook in 2017.[43] Comments posted over a 4 month period were categorised as positive, negative, unknown or questions. The comments categorised as unknown were neither negative nor positive and were excluded from the analysis. Tagged comments were also excluded.

Of the 2,837 comments posted during the study period, 525 (18.5%) were positive, 179 (6.3%) were negative, 215 (7.6%) were unknown, 71 (2.5%) were questions and 1,847 (65.1%) were tagged comments. Sixty-three comments (12%) were from users wanting to undergo the Cytosponge™ test or asking about availability in their country. Thirty-four people (6.5%) felt that the Cytosponge™ test appeared easier and less uncomfortable than endoscopy. Twelve people (2.3%) felt that the test appeared less invasive than endoscopy.

The most common theme among negative comments was around the risk of gagging or vomiting when the device was removed (n=49, 27.4%). Thirty people (16.8%) described the Cytosponge™ as looking uncomfortable or unattractive. Ten people (5.6%) commented on the risk of the sponge detaching from the string. Eight people (4.5%) wondered about other potential harms.

The study authors acknowledged that Facebook users were not likely to accurately represent the general population or older patients who might receive the Cytosponge™ test.

Cost effectiveness

All of the cost-effectiveness evidence on capsule sponge technologies relates to the Cytosponge™ device.

Existing literature

Five economic studies – four cost utility analyses and one budget impact analysis (BIA) – were identified.[44-48] We excluded one cost utility analysis on the basis that critical information required to assess the generalisability of its results were not available.[45] The BIA was also excluded as it is only available in poster format, with very limited information on the methods making an appraisal of study validity infeasible.[47]

Screening for Barrett's oesophagus in primary care patients with chronic reflux

The most recent cost-utility analysis compared screening using Cytosponge™-TFF3 testing with usual care in NHS England for the diagnosis of Barrett's oesophagus in primary care patients on long term treatment for GORD.[48] This study used data from the BEST3 trial.

The intervention was defined as screening with Cytosponge™-TFF3 testing, followed by a confirmatory endoscopy for TFF3 positive patients. The comparator was usual care, defined as referral for endoscopy as deemed necessary by the primary care physician. The analysis considered costs and health effects over a lifetime time horizon based on an initial patient age of 69 years. The perspective of the analysis was the NHS. A discount rate of 3.5% per annum was applied to costs and health effects.

A Markov model was used to conceptualise the disease process and decision problem. Patients enter either a treatment or natural history model and the costs of screening are applied. The number of patients entering the model at different stages of disease (no Barrett's oesophagus, non-dysplastic Barrett's oesophagus, low grade dysplasia, high grade dysplasia or oesophageal adenocarcinoma) was based on data from the BEST3 trial. All patients entering the treatment model received treatment for Barrett's oesophagus. Where treatment was successful, patients transitioned to the no Barrett's oesophagus state. Patients identified as true positives by endoscopy enter the treatment model. All other patients, including any false negatives, enter the natural history model. False positive patients incurred the cost of testing but no treatment costs.

The prevalence of Barrett's oesophagus in the study cohort was estimated at 9%. Natural history transition probabilities were drawn from the published literature. The effectiveness of treatment using radiofrequency ablation (RFA) and endoscopic mucosal resection (EMR) were taken from published sources. The effectiveness of oesophagectomy was estimated using 90-day mortality data from a national oesophageal adenocarcinoma audit.

The costs of screening using Cytosponge™-TFF3 testing were conservative (high) estimates based on introducing Cytosponge™ on a limited adoption basis. Costs included the device, centralised laboratory processing, the TFF3 antibody, manual pathology reporting costs, confirmatory endoscopy and the time of the nurse administering the test. Treatment costs included proton pump inhibitors and histamine receptor antagonists, endotherapy, oesophagectomy, chemotherapy and palliative care. Unit costs were taken from published sources. Palliative care costs were applied to anyone who died of late (stage 4) oesophageal adenocarcinoma. The study authors calculated mean costs for both arms of the model for each cost component and all components combined. The endoscopy costs were from UK tariffs.

Utilities and disutilities were derived from the literature. Disutilities were applied for stricture (2 weeks), perforation, EMR and RFA surgery (4 weeks), chemotherapy (4.5 months), and oesophagectomy (3 months).

In the base case analysis there were 1,654 Cytosponge™ tests and 198 confirmatory endoscopies, giving a total cost of £524,716, or £77 per GORD patient. In the usual care arm, there were 16 endoscopies at a total cost of £7,808 or £1 per GORD patient. The cost of one round of Cytosponge™-TFF3 testing, including treatment for Barrett's oesophagus and oesophageal adenocarcinoma, and palliative care, was an incremental £82 per GORD patient compared with usual care. The Cytosponge™ arm generated an additional 0.015 QALYs per patient. The incremental cost-effectiveness ratio (ICER) was £5,500 per QALY gained.

The deterministic sensitivity analysis (DSA) showed that there were a number of parameters that had a relatively large effect on the ICER. The parameters that had the largest impact were:

- the utility of the no Barrett's oesophagus health state (ICER range £3,756 to £10,268 per QALY gained)
- the average starting age of the patients (ICER range £1,952 to £8,286 per QALY gained)
- the prevalence of Barrett's oesophagus (ICER range £4,352 to £18,256 per QALY gained)
- the utility of the low grade dysplasia health state (ICER range £4,488 to £7,102 per QALY gained)
- the cost of Cytosponge™ (ICER range £3,788 to £7,212 per QALY gained)
- the uptake rate of Cytosponge™ (ICER range 5,008 to £7,742 per QALY gained).

A probabilistic sensitivity analysis (PSA) was used to estimate the uncertainty around the base case estimates for the incremental mean cost and incremental mean number of QALYs per patient. For the Cytosponge™ arm, these were an average of £582 [standard deviation (SD) £313] and 9.92 QALYs (SD 0.44). For the usual care arm, these were an average of £504 (SD £306) and 9.91 QALYs (SD 0.44). This gives an incremental cost of £78 (SD £86) and 0.015 QALYs (SD 0.002), giving an ICER of £5,405 (95% CI £6,791 to £17,600) per QALY gained. At a willingness to pay threshold of £20,000 per QALY gained, the probability that Cytosponge™-TFF3 testing was cost effective relative to usual care was 97%.

The second study compared no screening, screening using Cytosponge™-TFF3 testing, and screening using endoscopy only, for the detection of Barrett's oesophagus in male patients with symptoms of GORD.[46] The study authors used a male cohort because there were too few female patients in the BEST2 study to inform the performance characteristics of Cytosponge™-TFF3 testing in women.[31] Results for female patients were investigated in a scenario analysis.

Only results for the no screening and screening using Cytosponge™-TFF3 testing strategies are reported here since no endoscopy screening programme for Barrett's oesophagus exists in Scotland. For the no screening strategy, no intervention was assumed until patients were found to have cancer, at which point they received standard treatment. For the screening Cytosponge™-TFF3 testing strategy, patients with GORD symptoms were given a single Cytosponge™ test and a confirmatory endoscopy if they had a positive test result.

The analysis considered costs and health effects over a lifetime time horizon (until death or age 100) based on a patient starting age of 60 years. A US societal perspective was adopted and a discount rate of 3% per annum applied.

Two previously validated microsimulation models were used to generate results. Both models incorporate the full natural history of oesophageal adenocarcinoma, starting from normal health and progressing through non-dysplastic Barrett's oesophagus, low grade dysplasia and high grade

dysplasia before developing cancer. Diagnostic accuracy for Cytosponge™-TFF3 testing and endoscopy were derived from the BEST2 study and the published literature respectively. The model did not account for uptake rates in either strategy.

The cost of the Cytosponge™ device used in the analysis ($182/£149) was based on communication with the manufacturer and Medicare facility payments for comparable diagnostic tests. The cost of endoscopy and endoscopic eradication therapy (EET) for Barrett's oesophagus with high grade dysplasia were estimated using Medicare reimbursement rates. Costs for cancer treatment were derived from the published literature. Utilities for oesophageal adenocarcinoma by stage and disutilities for endoscopy, EET and complications, were estimated from the published literature.

Base case results found that ICERs for screening using Cytosponge™ ranged between $26,358 (£21,690) and $33,307 (£27,409) per QALY gained across the two models. A scenario analysis for female patients found ICERs ranging between $86,850 (£70,923) and $89,674 (£73,229) per QALY gained across the two models. The study authors note that results for female patients should be regarded as provisional because the data were based on a predominantly male cohort.

A DSA indicated that results were relatively sensitive to:

- the cost of the Cytosponge™ device (graphical presentation only)
- the sensitivity and specificity of Cytosponge™ [lower bounds $29,172 (£23,919) to $34,758 (£28,499) per QALY gained across models]
- the effectiveness of RFA [lower bounds $29,172 (£23,891) to $41,981 (£34,427) per QALY gained across models]
- the recurrence rate of Barrett's oesophagus after RFA [upper bounds $27,583 (£22,627) to $34,709 (£28,472) per QALY gained across models].

The third analysis was similar to the study reported in the paragraphs above. It compared no screening, screening using Cytosponge™-TFF3 testing and screening using endoscopy only, for the detection of Barrett's oesophagus in men with GORD symptoms.[44] No results were estimated for female patients. Only results for the no screening and screening using Cytosponge™-TFF3 testing strategies are reported here.

The no intervention and screening arms of the model were the same as the study above. A lifetime time horizon (age 100 years or death) was used, with a patient starting age of 50 years and a cycle length of 30 days. The perspective of the analysis was the UK NHS. Cost estimates were reported in US dollars for publication. An annual discount rate of 3.5 % was applied.

The model comprised of a decision tree (for screening and treatment) followed by a semi-Markov cohort model (for disease progression, screening and management strategies). Stages of disease were defined in the same way as the model described above. The model in this study also included

treatment, after treatment and death as discrete states. The management of non-dysplastic Barrett's oesophagus or low grade dysplasia was by follow-up endoscopy. Patients with high grade dysplasia or intramucosal cancer were treated by radical endotherapy. Patients with symptomatic oesophageal adenocarcinoma considered treatable underwent oesophagectomy.

A population prevalence of 8% for Barrett's oesophagus among screening invitees was assumed based on published literature. Estimates of between-state transition rates and the utility associated with each state were based the 2010 National Institute for Health and Clinical Excellence (NICE) guideline development group estimates. The cost of Cytosponge™ screening was based on the authors knowledge of manufacturing costs ($15/£12 per device), test administration (including staff time costs of $11/£9 per test), and laboratory costs ($61/£50 test), based on the BEST study.[30] All other costs in the main analysis relate to published reference costs during 2007–2008 for NHS England.

Results of the base case analysis found that, compared with no screening, screening using Cytosponge™-TFF3 testing was associated with an incremental discounted total cost of $240 (£197) per patient and incremental discounted total QALYs of 0.015 per patient, resulting in an ICER of $15,724 (£12,889) per QALY gained.

A PSA estimated that screening using Cytosponge™ had a 94% probability of being cost effective at a willingness to pay threshold of $45,000 (£36,883) per QALY gained.

Patients with chronic reflux referred to secondary care for an endoscopy

An unpublished cost-effectiveness analysis from NHS England compared Cytosponge™ as a triage tool for patients with low risk reflux symptoms referred for endoscopy with usual care.[39] This study was conducted using data from a pilot project discussed in the NHS data analysis section.

The intervention was defined as Cytosponge™-TFF3 and p53 testing alongside cytological assessment for cellular atypia. Patients with a positive Cytosponge™ result had a confirmatory endoscopy. The comparator was usual care, defined as endoscopy. The analysis considered costs and health effects over a lifetime time horizon based on an initial patient age of 52 years. The perspective of the analysis was that of NHS England and a discount rate of 3.5% per annum was applied.

A Markov model was used to conceptualise the disease process and decision problem. The model structure was composed of two distinct phases. Phase 1 comprised the short term diagnostic pathway that captured time from referral for endoscopy to receipt of test results. Phase 2 represented the clinical pathway after receiving test results. Disease stages and other discrete states in the model were the same as the third study described in the section above. Monitoring and treatment costs associated with each health state were included.

Patient characteristics at the start of the model were informed by data collected during the pilot. The sensitivity of Cytosponge™ testing was based on the BEST2 study. The sensitivity of endoscopy

was assumed to be 100% (gold standard) for the purposes of the analysis. Between-state transition rates were based on estimates in the published literature. Health state utility values were informed by previously published cost-effectiveness analyses. The cost of the Cytosponge™ test was based on data collected during the pilot.

Results of the base case analysis found that, compared with usual care, triage using Cytosponge™ was associated with an incremental discounted total cost of -£421.57 per patient and incremental discounted total QALYs of -0.0041 per patient.

The study authors conducted a BIA to estimate the short term affordability of using Cytosponge™ as a triage tool compared to usual care in the eligible patient population. They estimated that there would be 15,121 patients eligible for Cytosponge™ testing in year 1, increasing to 17,019 patients by year 5, based on data from the pilot and diagnostic waiting times. A range of estimates of the net budget impact were provided using different assumptions regarding uptake during the 5 year time period. Applying an uptake rate of 10% in year 1 and 50 % in year 5, resulted in a net budget impact estimate of -£0.6 million in year 1 rising to -£3.6 million in year 5 (that is, cost saving). Using an uptake rate of 90% in year 1 and 100% in year 5, resulted in a net budget impact estimate of -£5.7 million in year 1 rising to -£7.1 million in year 5.

SHTG BIA: patients with chronic reflux symptoms referred for endoscopy

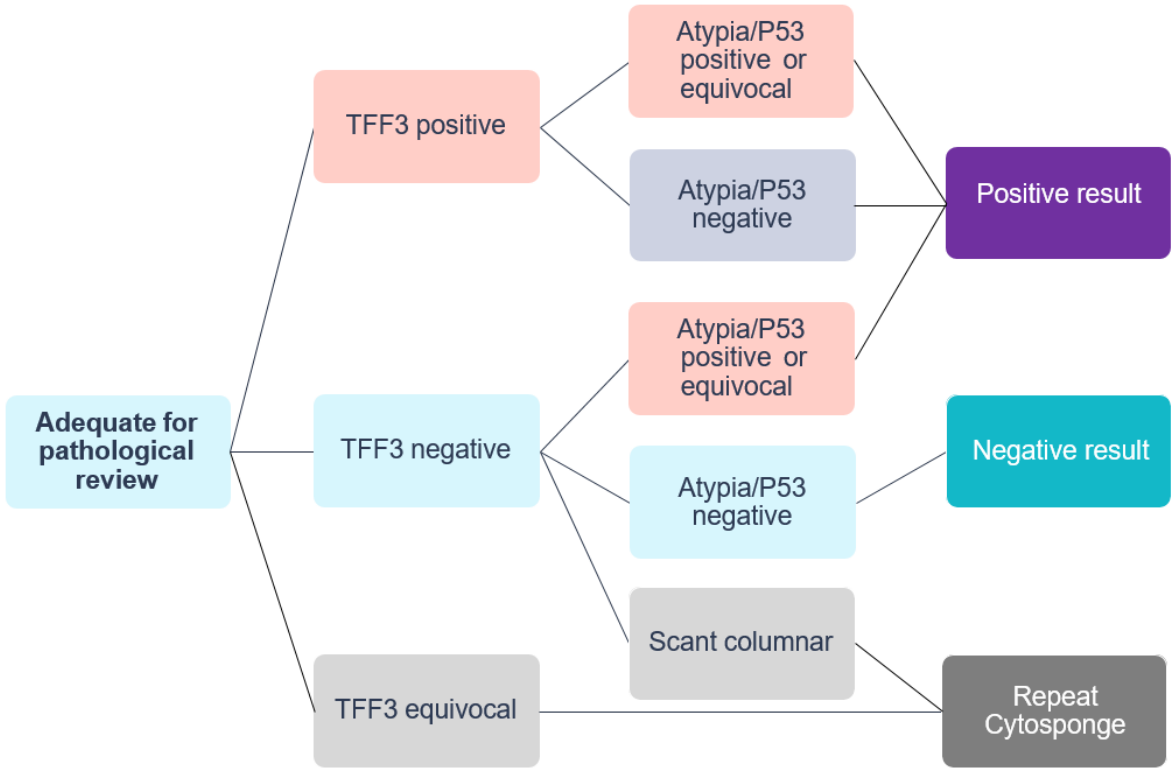
We conducted a BIA to estimate the effects of introducing capsule sponge testing compared with usual care (endoscopy) for the detection of Barrett's oesophagus in NHSScotland. The patient population was defined as individuals with chronic GORD symptoms referred to secondary care for an endoscopy.

The BIA does not apply to the use of capsule sponge technologies for surveillance of patients with diagnosed Barrett's oesophagus. We are unable to provide a BIA for these patients because of the complexity of the clinical pathways and uncertainties about patient numbers.

The intervention was defined as capsule sponge cell sampling, laboratory based testing and cytological assessment, followed by a confirmatory endoscopy for patients with a positive test result. Capsule sponge procedures were assumed to be conducted by a trained nurse at patients' local secondary care centre. The comparator was usual care, defined as endoscopy that was assumed to be conducted at patients' local secondary care centre.

A capsule sponge result was determined by two laboratory tests (TFF3 and p53) and cytological assessment of cellular atypia. Our understanding is that laboratory testing, cytological assessment and reporting of results are provided by Cyted Ltd and included in the cost of capsule sponge technologies quoted to the Scottish Government. A visual representation of how the results of the laboratory tests and cytological assessment are combined for interpretation in terms of positive, negative or inconclusive results is shown in *Figure 1*.

Figure 1: Criteria for positive, negative and inconclusive capsule sponge results



TFF3 = trefoil factor 3; p53 = tumour protein 53

Model structure

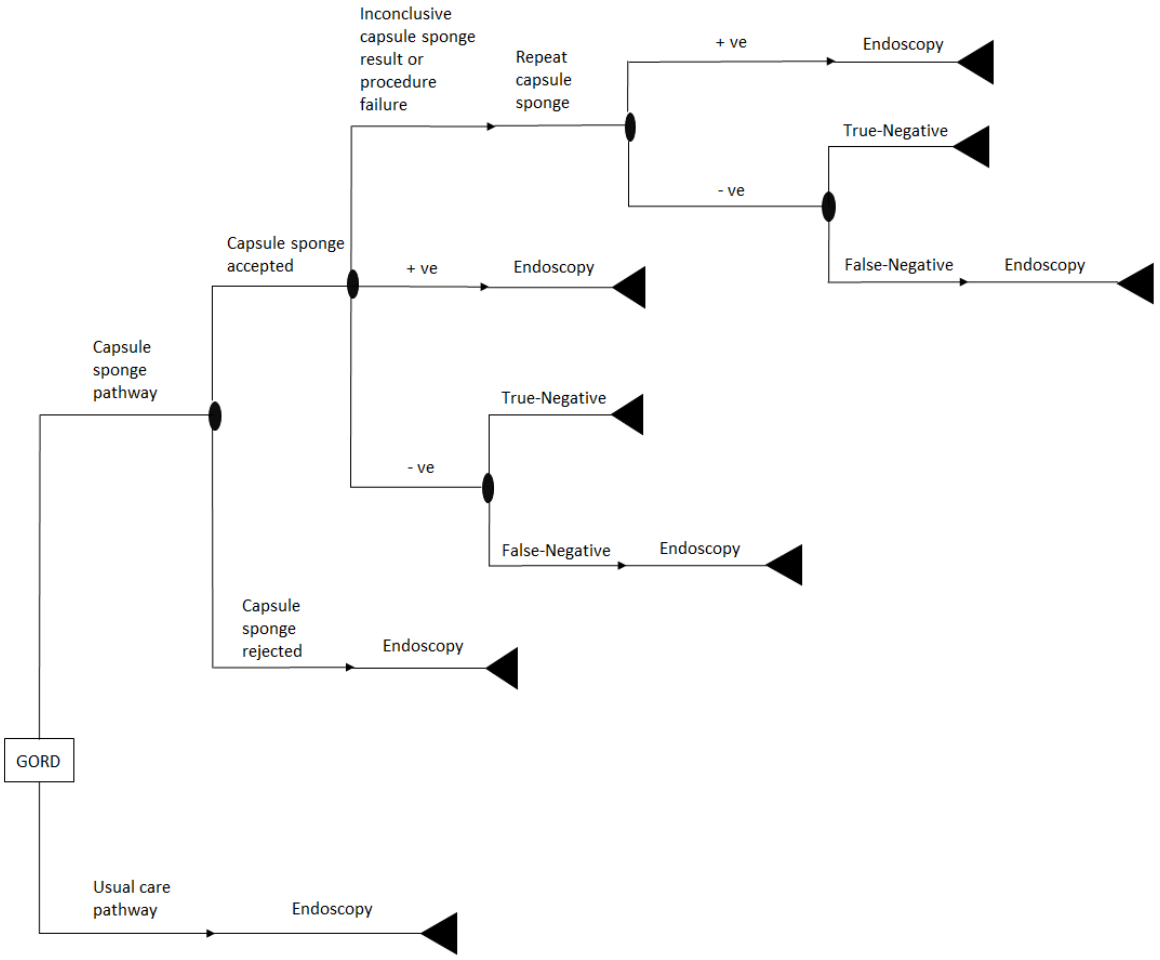
A condition-specific cohort model in the form of a decision tree was used to estimate the average cost of the capsule sponge and usual care pathways. A visual overview of the model is provided in *Figure 2.*

For the capsule sponge arm, patients are initially offered a capsule sponge test. Patients who accept this offer undergo the test and have one of four results: negative, positive, inconclusive or a procedure failure (insufficient cells collected for testing). Patients with a positive result have a confirmatory endoscopy. Patients with a true negative result (correctly identified as not having Barrett's oesophagus) receive no further investigation. Patient with a false negative result (incorrectly identified as not having Barrett's oesophagus) are assumed to receive a repeat referral from their primary care physician and undergo endoscopy. Where an inconclusive result was generated or a procedure failure occurred, patients received a repeat capsule sponge test that was assumed to collect sufficient cells and to generate a conclusive result. Depending on the outcome of this repeat capsule sponge test, patients received either no further investigation or a confirmatory endoscopy. Patients who rejected the offer of a capsule sponge test were assumed to undergo endoscopy.

For the usual care arm, all patients were assumed to undergo endoscopy.

The model incorporates the cost of healthcare resources from referral to diagnosis or exclusion of Barrett's oesophagus only. The model does not account for the cost of healthcare resources incurred beyond this point in the clinical pathway.

Figure 2: Model structure overview



GORD = gastro-oesophageal reflux disease; +ve = positive; -ve = negative

Input data

The clinical and cost data used in the base case BIA are presented in *Table 10*.

The total annual number of Scottish patients with chronic GORD symptoms who have a test to diagnose or exclude Barrett's oesophagus is unknown. The size of the eligible population was estimated by combining data on the total number of upper gastro-intestinal endoscopies in Scotland 2019–2020 (76,324) and estimates of the proportion of upper gastro-intestinal endoscopies conducted because of GORD symptoms in the published literature.[49] This approach assumes that all patients referred for upper gastro-intestinal endoscopy undergo one procedure each. It is possible that the size of the total eligible population is overestimated.[19 48] The prevalence of Barrett's oesophagus in this patient population was informed by the published literature.[20]

The proportion of patients that accept a capsule sponge test was based on clinical expert opinion (Professor Grant Fullarton, Consultant Surgeon and Associate Professor of Surgery, NHS Greater Glasgow and Clyde. Personal communication, 12 October 2023). The proportion of positive and negative test results was informed by our evaluation of data on Cytosponge™. The same data were used to estimate the proportion of inconclusive test results and procedures that failed to collect sufficient cells testing.

The sensitivity of a capsule sponge test was set as the pooled estimate reported in the systematic review reported in the clinical effectiveness section. It was assumed that endoscopy has a sensitivity of 100% (gold standard) for the purposes of this analysis.

The cost of a capsule sponge test was estimated using a microcosting approach. The device and pathology reporting price of EndoSign® for NHSScotland was used. Data on the average time spent by a nurse administering capsule sponge tests (20 minutes) reported in the published literature was combined with the unit cost for this healthcare professional (£52 per hour) reported in the *Unit Costs of Health and Social Care 2022 Manual*.[50] Prices for EndoSign® were used in the analysis based on our understanding that NHSScotland is likely to use this device for the foreseeable future (Professor Grant Fullarton, Consultant Surgeon and Associate Professor of Surgery, NHS Greater Glasgow and Clyde. Personal communication, 25 October 2023). The cost of an endoscopy procedure including biopsies was taken from the *National Schedule of NHS Costs 2021/22* for NHS England.[51]

Capital investment costs were excluded from the analysis based on our understanding that the necessary infrastructure (endoscopy units, clinic space, etc) is already available across NHSScotland.

Table 10: Model input data

Parameters	Usual care	Capsule sponge	Source
Clinical inputs			
Total eligible population	24,576 patients		Total number of upper gastrointestinal endoscopies across NHSScotland 2019/2020: 76,324 procedures[52] Proportion of upper gastrointestinal endoscopies because of GORD symptoms: 32.2% (mid-point)[49]
Prevalence of Barrett's oesophagus	0.175		Healthcare Improvement Scotland report[20]
Sensitivity of capsule sponge test	NA	0.810	Systematic review by Iqbal et al (2018)[27]
Proportion of patients offered capsule sponge procedures that accept	NA	0.950	Clinical expert opinion (Professor Grant Fullarton, Consultant Surgeon and Associate Professor of Surgery, NHS Greater Glasgow and Clyde. Personal communication, 12 October 2023)
Proportion of patients offered capsule sponge procedures that decline	NA	0.050	1 minus the proportion assumed to accept
Proportion of positive capsule sponge test results	NA	0.101	SHTG analysis of data collected during Cytosponge™ pilot in Scotland
Proportion of negative capsule sponge test results	NA	0.899	
Proportion of inconclusive capsule sponge results or procedures that failed (insufficient cells collected)	NA	0.103	
Costs inputs			
EndoSign® procedure (device, processing, TFF3, immunostaining, reporting, administration and overheads)	NA	£287.33	NHSScotland acquisition price from Scottish Government HCP time and overhead costs: PSSRU, Unit Costs of Health and Social Care (2022)[50]/Swart et al (2021)[48]
Upper endoscopy procedure including biopsies (device, processing, administration and overheads)	£692.85	£692.85	National schedule of NHS costs 2021/22 (NHS England)[51] Diagnostic endoscopic upper gastrointestinal tract procedures with biopsy, 19 years and over. FE21Z. Day case.

NA = not applicable; SHTG = Scottish Health Technologies Group; PSSRU = Personal and Social Services Research Unit; HCP = healthcare professional

Results

The base care results, based on 100% adoption of capsule sponge testing across NHSScotland, are presented in *Table 11*. The results indicate that the cost of providing capsule sponge testing to the total eligible population in Scotland is £10.4 million compared with £17.0 million for usual care, giving an incremental cost saving of £6.6 million per year.

These figures represent the value of healthcare resources (measured in monetary terms) attributable to the capsule sponge and usual care pathways. The majority of healthcare resources included in these figures, such as staff resources and endoscopy equipment costs, are expected to be fixed over the short term. Since staff are likely to still be employed within the NHS, and endoscopy equipment is likely to still be used, capsule sponge testing is not expected to provide cash releasing savings of this magnitude during the time period considered.

Table 11: Base case results from the BIA for total eligible population

Pathway	Cost	Incremental cost
Usual care	£17.0m	-
Capsule sponge	£10.4m	-£6.6m

Note: *figures rounded to the nearest £100k*

Disaggregated analyses of these results, in terms of the quantities and costs for each resource category, are presented in *Tables 12 and 13*. The analysis indicates that the total number of endoscopy procedures per year is expected to decrease by 20,213 if a complete roll out of capsule sponge testing is introduced. This is because of the ability of capsule sponge tests to triage patients who require endoscopy and equates to a cost saving of £14.0 million. The use of capsule sponge testing represents an incremental cost of £7.4 million.

Table 12: Disaggregated analysis of base case quantities of resource use for eligible patients

	N procedures for total eligible patient population		
Resource	**Usual care**	**Capsule sponge**	**Incremental**
Endoscopy (standard)	24,576	NA	-24,576
Endoscopy (confirmatory)	NA	2,358 (54.0%)	2,358
Endoscopy (because declined capsule sponge)	NA	1,229 (28.2%)	1,229
Endoscopy (because of false negative capsule sponge result)	NA	776 (17.8%)	776
Endoscopy (total)	**24,576**	**4,363**	**-20,213**
Capsule sponge (standard)	NA	23,348 (90.7%)	23,348
Capsule sponge (repeated because of inconclusive result or failure to collect sufficient cells)	NA	2,405 (9.3%)	2,405
Capsule sponge (total)	**0**	**25,752**	**25,752**

Table 13: Disaggregated analysis of base case costs for eligible patients by resource category

	Cost for total eligible population		
Resource	**Usual care**	**Capsule sponge**	**Incremental**
Endoscopy (standard)	£17.0m	NA	-£17.0m
Endoscopy (confirmatory)	NA	£1.6m	£1.6m
Endoscopy (because declined capsule sponge)	NA	£0.9m	£0.9m
Endoscopy (because of false negative capsule sponge result)	NA	£0.5m	£0.5m
Endoscopy (total)	**£17.0m**	**£3.0m**	**-£14.0m**
Capsule sponge (standard)	NA	£6.7m	£6.7m
Capsule sponge (repeated because of inconclusive results or failure to collect sufficient cells)	NA	£0.7m	£0.7m
Capsule sponge (total)	**0**	**£7.4m**	**£7.4m**
Total cost	**£17.0m**	**£10.4m**	**-£6.6m**

Note: *figures rounded to the nearest £100k*

Sensitivity analysis

Sensitivity analyses were conducted to investigate the impact of changing the clinical inputs of the model. The boundary values for these model inputs were informed by lower and upper values reported in the published literature where available. Boundary values for the remaining model inputs are based on assumptions.

The results of the sensitivity analyses are presented in *Table 14*. They indicate that incremental costs associated with the adoption of capsule sponge testing are most sensitive to the size of the total eligible population (scenarios 1a and 1b).

Table 14: Sensitivity analysis results

Scenario	Description		Cost		Incremental cost
			Usual care	Capsule sponge	
0	**Base case**		**£17.0m**	**£10.4m**	**-£6.6m**
1a	Total eligible population	18,089	£12.5m	£7.7m	-£4.8m
1b		31,064	£21.5m	£13.2	-£8.3m
2a	Prevalence of Barrett's oesophagus	0.150	£17.0m	£10.3m	-£6.7m
2b		0.200	£17.0m	£10.5m	-£6.5m
3a	Sensitivity of capsule sponge test	0.729	£17.0m	£10.7m	-£6.3m
3b		0.891	£17.0m	£10.2m	-£6.8m
4a	Proportion of patients offered capsule sponge procedure that accept	0.900	£17.0m	£10.8m	-£6.2m
4b		1.000	£17.0m	£10.1m	-£6.9m
5a	Proportion of inconclusive capsule sponge results or procedures that failed (insufficient cells collected)	0.087	£17.0m	£10.3m	-£6.7m
5b		0.119	£17.0m	£10.5m	-£6.5m
6a	Proportion of positive capsule sponge test results	0.085	£17.0m	£10.2m	-£6.8m
6b		0.117	£17.0m	£10.7m	-£6.3m

Note: *figures rounded to the nearest £100k*

Budget impact: phased over 5 years

The figures outlined in *Tables 11-14* indicate the expected change in annual expenditure and resource use, under a range of assumptions, following a complete roll out (100% adoption) of capsule sponge testing across NHSScotland. It is anticipated that adoption of capsule sponge testing across NHSScotland will gradually increase each year, meaning that the changes in expenditure and resource use will be lower than estimated in *Tables 11-14* in the short term.

The figures in *Table 15* present the expected change in expenditure over a time period of 5 years assuming an initial uptake rate of 10% (year 1), rising by 10 percentage points each year to 50% by year 5, for a range of estimates of the size of the total eligible population. These results indicate that, using the base case estimate for the size of the total eligible population (24,576 patients), the incremental cost of capsule sponge testing in year 1 is -£0.7m (that is, cost saving), rising to -£3.3m in year 5. Scenarios 1a and 1b, using a lower and higher estimate of the size of the total eligible population respectively, indicate uncertainty around these figures.

The figures in *Table 15* represent the value of healthcare resources (measured in monetary terms) attributable to the capsule sponge and usual care pathways. The majority of healthcare resources included in these figures, such as staff resources and endoscopy equipment costs, are expected to be fixed over the short term. Since staff are likely to still be employed within the NHS, and endoscopy equipment is likely still to be used, capsule sponge testing is not expected to provide cash releasing savings of this magnitude during the time period considered.

The results of our BIA are very similar to the estimates from NHS England who are expected to have a much larger eligible patient population.[39] It is likely this similarity arises because of differences in how our BIA and the English analysis have calculated the eligible patient population.

Table 15: Base case BIA estimate over a 5 year time period

Year	1	2	3	4	5
Base case: total eligible population = 24,576 patients					
Total number of patients	2,458	4,915	7,373	9,831	12,288
Net budget impact	-£0.7m	-£1.3m	-£2.0m	-£2.6m	-£3.3m
Scenario 1a: total eligible population = 18,089 patients					
Total number of patients	1,809	3,618	5,427	7,236	9,044
Net budget impact	-£0.5m	-£1.0m	-£1.5m	-£2.0m	-£2.4m
Scenario 1b: total eligible population = 31,064 patients					
Total number of patients	3,106	6,213	9,319	12,426	15,532
Net budget impact	-£0.8m	-£1.7m	-£2.5m	-£3.3m	-£4.2m

Note: *figures rounded to the nearest £100k*

Assumptions/limitations

The BIA is based on the assumptions outlined in *Table 16.*

The BIA is subject to a number of limitations, partly because of the assumptions made in its construction. These limitations are listed below.

- The total number of patients who receive a diagnostic procedure to diagnose or exclude the presence of Barrett's oesophagus per year because of chronic GORD symptoms across NHSScotland is unknown. The implication of this for the BIA is that estimates regarding the size of the total eligible population are imprecise, resulting in large variations in budget impact estimates.
- Capsule sponge test results and procedure failures were informed using data collected during the implementation period of the Cytosponge™ device across NHSScotland, which may bias results because of the non-experimental design of the data collection process.
- Endoscopy was assumed to have an effective sensitivity of 100% for the purposes of the analysis. Recent research has suggested that endoscopy does not exhibit this degree of accuracy in practice.[53]

- Budget impact estimates were based on assumptions regarding the current and future provision of capsule sponge testing over a time period of 5 years. If provision of capsule sponge testing across NHSScotland is significantly different from that assumed, this could have a significant impact on results.

Table 16: Assumptions made in our BIA

Input	Assumption
Proportion of upper gastro-intestinal endoscopies because of GORD symptoms	The proportion of upper gastro-intestinal endoscopies conducted because of GORD symptoms reported in the published literature for the United States is generalisable to NHSScotland[49]
Proportion of patients offered capsule sponge procedure that accept	The proportion of patients accepting capsule sponge procedures estimated by clinical expert opinion is generalisable to the Scottish population.
Sensitivity of capsule sponge tests	The pooled estimate of sensitivity for Cytosponge™ reported in the systematic review by Iqbal et al[27] is generalisable to the EndoSign® device.
Probability of false negative patients undergoing endoscopy	All patients who receive a false negative capsule sponge test result re-present to secondary care and undergo endoscopy.
Proportion of inconclusive capsule sponge results or procedures that failed (insufficient cells collected)	The proportion of Cytosponge™ procedures that generate inconclusive results or fail to collect sufficient cells (prompting a repeat capsule sponge procedure) estimated by our analysis of data collected during the pilot of Cytosponge™ in NHSScotland is generalisable to use of the EndoSign® device in the defined patient population.
Proportion of positive capsule sponge test results	The proportion of positive capsule sponge test results estimated by our analysis of data collected during the pilot of Cytosponge™ in NHSScotland is generalisable to the use of the EndoSign® in the defined patient population.
Maximum number of endoscopies in usual care arm	The maximum number of endoscopies for patients in the usual care arm is assumed to be one.
Healthcare resource use for patients who decline invitation for capsule sponge procedure	Patients who decline the offer of a capsule sponge procedure are assumed to undergo endoscopy.
Maximum number of capsule sponge tests	If the standard capsule sponge test is inconclusive or fails to collect sufficient cells, patients are assumed to undergo one extra capsule sponge test that successfully collects sufficient cells for analysis and produces a conclusive result.

Conclusion

Capsule sponge in patients with chronic reflux

A systematic review estimating the diagnostic accuracy of Cytosponge™ reported a sensitivity of 81% and specificity of 91% for detecting Barrett's oesophagus in patients with chronic reflux. This means that 19% of patients tested would be wrongly told they did not have Barrett's oesophagus. Nine percent of patients would be diagnosed with Barrett's oesophagus when they did not have the condition.

In NHS England, Cytosponge™ triage of patients with chronic reflux who were referred to secondary care for an endoscopy, resulted in an estimated 78% of patients being removed from the endoscopy waiting list. These results suggest that capsule sponge testing is an effective triage tool for patients with chronic reflux referred to secondary care.

Three economic analyses comparing screening using Cytosponge™-TFF3 with no screening or usual care in patients with GORD symptoms found Cytosponge™ to be cost effective. These studies were all in a primary care screening population that is not currently eligible for capsule sponge testing in Scotland.

In NHS England, the use of Cytosponge™ as a triage tool for patients with chronic reflux referred for an endoscopy was moderately less costly but marginally less effective than usual care (endoscopy).

The base case results of our BIA comparing capsule sponge testing with usual care in people with chronic reflux symptoms referred for an endoscopy estimated an incremental cost saving of £0.7 million in year one, rising to £3.3 million in year five. These estimates are sensitive to the size of the eligible population. Capsule sponge testing is not expected to provide cash releasing savings of this magnitude during the time period considered, but may help reduce endoscopy waiting lists.

Capsule sponge in patients with Barrett's oesophagus

In a cross-sectional study, Cytosponge™ plus biomarker analysis had a sensitivity of 89% and a specificity of 84% for detecting high grade dysplasia or oesophageal cancer in patients with Barrett's oesophagus. This means that 11% of patients would be wrongly told they do not have dysplasia or cancer. Six percent of patients would be incorrectly diagnosed with dysplasia or cancer. These diagnostic accuracy results should be considered in the context of recent evidence suggesting that the reference standard (endoscopy) is not 100% accurate. Published studies indicate that endoscopy misses 21% to 23.5% of oesophageal adenocarcinomas in patients previously diagnosed with Barrett's oesophagus.[53, 54]

Two observational studies demonstrated the utility of Cytosponge™ for triaging patients with Barrett's oesophagus for endoscopy. A substantial proportion of patients (approximately 65 %) were

classed as low risk and could potentially be removed from endoscopy waiting lists. The frequency and type (endoscopy or Cytosponge™) of surveillance testing could be decided based on Cytosponge™ test results.

In our evaluation of data from Scottish health boards, the average time from last endoscopy to treatment was 1,538 days and from Cytosponge™ test to treatment was 244 days for patients with Barrett's oesophagus under surveillance.

In an unpublished study of data from NHSScotland, half of the patients considered high risk for cancer received an endoscopy within 3 months of their Cytosponge™ test. Introducing Cytosponge™ led to significant reductions in delays to patient surveillance (4 month reduction) and the proportion of patients who had their surveillance delayed by more than 3 months (15.5% reduction).

We were unable to provide a cost-effectiveness analysis for patients with Barrett's oesophagus because of a lack of data.

Safety of capsule sponge devices

Adverse events associated with the Cytosponge™ device include a sore throat, indigestion or reflux and oesophageal or gastric pain. Serious adverse events associated with Cytosponge™ include the string breaking and bleeding after withdrawal of the device. Few serious adverse events relating to the Cytosponge™ were reported in primary studies. There is some debate about whether these adverse events meet the criteria for a 'serious' event set out by international safety agencies.

In 2023, Medtronic recalled several batches of Cytosponge™ devices that had a higher than expected rate of detachment from the string.

A small proportion of patients (approximately 3.5%) in most studies were unable to swallow the Cytosponge™. Failure to swallow the device was more common in patients with Barrett's oesophagus and patients tested in secondary care. Assessment by endoscopy nurses could help identify patients eligible for a capsule sponge test.

Acceptability

The acceptability of the Cytosponge™ test was generally high, with approximately 80% of patients willing to have the test again. The aspects of the test that caused the most concern were successfully swallowing and retrieving the device. Patients who had high or very high anxiety, were unable to swallow the Cytosponge™ device on the first try or who drank alcohol on most days, were more likely to have a poor experience of the Cytosponge™ test.

Cytosponge™ was more acceptable to patients than endoscopy without sedation, but less acceptable than endoscopy with sedation. Two studies exploring the views of the public on Cytosponge™ found that the main concern was around the risk of gagging or vomiting during the test.

Limitations of the evidence

All the published literature on capsule sponge technologies currently relates to the Cytosponge™ device. Since the EndoSign® device is very similar in design and function to the Cytosponge™ we have assumed that the evidence can be generalised to both devices. This needs to be confirmed in studies assessing the EndoSign® device.

Almost all the primary studies identified were conducted by researchers who were involved in developing the original Cytosponge™ and founding Cyted Ltd. This is a conflict of interest because the researchers publishing on this topic being involved in developing and marketing the technologies may have introduced an unknown degree of bias.

Identified research gaps

Studies that report on the diagnostic accuracy, effectiveness, safety and cost effectiveness of the EndoSign® device in patients with chronic reflux or Barrett's oesophagus are needed inform decisions on the transferability of evidence from existing Cytosponge™ studies.

It would be helpful to have clinical trials of capsule sponge devices, including both Cytosponge™ and EndoSign®, which are conducted by researchers who are not involved in the development or manufacture of either device to clarify any potential biases in existing studies.

Acknowledgements

Healthcare Improvement Scotland development team

- Mrs Rachel Alexander, Senior Project Officer
- Ms Uzma Aslam, Senior Project Officer
- Mr Guy Berg, Senior Health Economist
- Ms Jenny Harbour, Lead Author/Health Services Researcher
- Mr Paul Herbert, Health Information Scientist
- Dr Rachel Moss, Health Services Researcher
- Mr James Stewart, Programme Manager

Peer reviewers

SHTG Executive would like to thank the following individuals who took part in the peer review and provided comments on the draft document and recommendation.

- Dr Siobhan Chien, Clinical Research Fellow, NHS Golden Jubilee.
- Professor Rebecca Fitzgerald, Professor of Cancer Prevention, University of Cambridge.
- Professor Grant Fullarton, Consultant Surgeon and Associate Professor of Surgery, NHS Greater Glasgow and Clyde.
- Mr Paul Glen, Consultant Upper Gastrointestinal Surgeon, NHS Greater Glasgow and Clyde.
- Ms Neha Goel, Chief Operating Officer, Cyted Ltd.
- Dr Maria O'Donovan, Consultant Histopathologist, Cambridge University Hospitals NHS Trust.

Declarations of interest from all reviewers are published alongside the review on our website. Reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

We would like to thank the following people who supported our evaluation of Cytosponge™.

- Dr Siobhan Chien, Clinical Research Fellow, NHS Golden Jubilee.
- Professor Grant Fullarton, Consultant Surgeon and Associate Professor of Surgery, NHS Greater Glasgow and Clyde.
- Mr Tim Norwood, Data and Measurement Advisor, Healthcare Improvement Scotland.
- Mr Toby Stead, Data and Measurement Advisor, Healthcare Improvement Scotland.
- Dr Robert Van Der Meer, Professor of Management Science, University of Scotland.
- Mr Jason White, Head of Innovation, Centre for Sustainable Development, NHS Golden Jubilee.
- Ms Gayle Wylie, Programme Manager – Innovation, Centre for Sustainable Development, NHS Golden Jubilee.

Published November 2023

Suggested citation: Harbour J, Berg G, Moss R, Herbert P, Stewart J, Aslam U, Alexander R. (2023). Capsule sponge cell collection devices for the detection of pre-malignant (Barrett's oesophagus) or early stage oesophageal cancer. Glasgow/Edinburgh; NHS Healthcare Improvement Scotland. https://shtg.scot/our-advice/capsule-sponge-endoscopy-as-an-alternative-to-endoscopy-for-the-detection-of-pre-malignant-or-early-stage-oesophageal-cancer/

References

1. Watson RGP. Barrett's oesophagus: an overview. J R Coll Physicians Edinb. 2009;39:47-50.
2. CADTH. The Cytosponge: an alternative to endoscopy in detecting Barrett esophagus. 2015 [cited 2023 Nov 30]; Available from: https://www.cadth.ca/sites/default/files/pdf/EH0037_Cytosponge_e.pdf.
3. Cancer Research UK. What is Barrett's oesophagus? 2023 [cited 2023 Sept 04]; Available from: https://www.cancerresearchuk.org/about-cancer/other-conditions/barretts-oesophagus/about-barrett%27s.
4. Chettouh H, Mowforth O, Galeano-Dalmau N, Bezawada N, Ross-Innes C, MacRae S, et al. Methylation panel is a diagnostic biomarker for Barrett's oesophagus in endoscopic biopsies and non-endoscopic cytology specimens. Gut. 2018;67(11):1942-9.
5. Scottish Government. Healthcare innovation. 2020 [cited 2023 Nov 01]; Available from: https://www.gov.scot/news/healthcare-innovation/.
6. NHS Inform. Cytosponge. 2023 [cited 2023 Sept 08]; Available from: https://www.nhsinform.scot/tests-and-treatments/non-surgical-procedures/cytosponge.
7. Scottish Government. Innovative health technology helping patients. 2022 [cited 2023 Nov 01]; Available from: https://www.gov.scot/news/innovative-health-technology-helping-patients/.
8. Sanfrancesco J, Jones JS, Hansel DE. Diagnostically challenging cases: what are atypia and dysplasia? Urologic Clin North Am. 2013;40(2):281-93.
9. Marcovitch H. Black's medical dictionary. London: Bloomsbury Publishing PLC; 2009.
10. Cancer Research UK. High grade dysplasia of the oesophagus. 2023 [cited 2023 Sept 07]; Available from: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/stages-types-and-grades/stage-0#:~:text=High%20grade%20dysplasia%20means%20that,grow%20into%20the%20deeper%20layers.
11. NHS Inform. Gastro-oesophageal reflux disease. 2023 [cited 2023 Sept 08]; Available from: https://www.nhsinform.scot/illnesses-and-conditions/stomach-liver-and-gastrointestinal-tract/gastro-oesophageal-reflux-disease-gord.
12. NHS Inform. Oesophageal cancer. 2023 [cited 2023 Sept 08]; Available from: https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/oesophageal-cancer.
13. Cyted. Endosign. 2023 [cited 2023 Sept 27]; Available from: https://www.endosign.com/hcp/overview.
14. Yusuf A, Fitzgerald RC. Screening for Barrett's oesophagus: are we ready for it? Curr Treat Options Gastro. 2021;19(2):321-36.
15. National Institute for Health and Clinical Excellence (NICE). Cytosponge for detecting abnormal cells in the oesophagus: MIB240. 2020 [cited 2023 Nov 30]; Available from: https://www.nice.org.uk/advice/mib240/chapter/Summary.

16. Cyted Ltd. Endosign in action. 2023 [cited 2023 Nov 01]; Available from: https://www.endosign.com/hcp/endosign-in-action.
17. Landy R, Killcoyne S, Tang C, Juniat S, O'Donovan M, Goel N, et al. Real world implementation of non-endoscopic triage testing for Barrett's oesophagus during COVID-19. QJM. 2023;116(8):659-66.
18. National Institute for Health and Clinical Excellence (NICE). Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. 2019 [cited 2023 Sept 04]; Available from: https://www.nice.org.uk/guidance/cg184.
19. NICE Clinical Knowledge Summaries. Dyspepsia - proven GORD: how common is it? 2023 [cited 2023 Sept 04]; Available from: https://cks.nice.org.uk/topics/dyspepsia-proven-gord/background-information/prevalence/#:~:text=A%20systematic%20review%20of%20the,5%20per%201000%20person%2Dyears.
20. Healthcare Improvement Scotland. Radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia. Edinburgh; Healthcare Improvement Scotland: 2012.
21. Maroni R, Barnes J, Offman J, Scheibl F, Smith SG, Debiram-Beecham I, et al. Patient-reported experiences and views on the Cytosponge test: a mixed-methods analysis from the BEST3 trial. BMJ Open. 2022;12(4):e054258.
22. Ghimire B, Landy R, Maroni R, Smith SG, Debiram-Beecham I, Sasieni PD, et al. Predictors of the experience of a Cytosponge test: analysis of patient survey data from the BEST3 trial. BMC Gastroenterol. 2023;23(1):7.
23. Cancer Research UK. Oesophageal cancer statistics. c2023 [cited 2023 Sept 04]; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer#heading-Four.
24. Cancer Research UK. Oesophageal cancer incidence statistics. 2021 [cited 2023 Oct 19]; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/incidence#heading-Zero.
25. Public Health Scotland. Cancer mortality: annual update to 2021 - digestive organs. 2021 [cited 2023 Sept 01]; Available from: https://publichealthscotland.scot/publications/cancer-mortality/cancer-mortality-in-scotland-annual-update-to-2021/view-the-cancer-mortality-data-files/#Digestive%20organs.
26. Public Health Scotland. Cancer incidence and prevalance in Scotland (to December 2019). 2021 [cited 2023 Sept 04]; Available from: https://publichealthscotland.scot/media/7753/2021-05-11-cancer-incidence-report.pdf.
27. Iqbal U, Siddique O, Ovalle A, Anwar H, Moss SF. Safety and efficacy of a minimally invasive cell sampling device ('Cytosponge') in the diagnosis of esophageal pathology: a systematic review. Eur J Gastroenterol Hepatol. 2018;30(11):1261-9.
28. Lao-Sirieix P, Debiram-Beecham I, Sarah K, Gadeke L, Bincy A, O'Donovan M, et al. Evaluation of a minimally-invasive cytosponge esophageal cell collection system in patients with Barrett's esophagus. Gastroenterol. 2015;148(4):S-16.

29. Iyer MP, Johnson M, Lansing R, Yab TC, Taylor WR, Mahoney DW, et al. Assessment of sponge-on-string device parameters for the non-endoscopic detection of Barrett's esophagus: results from a randomized trial. Am J Gastroenterol. 2016;111:S229.

30. Kadri SR, Lao-Sirieix P, O'Donovan M, Debiram I, Das M, Blazeby JM, et al. Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. BMJ. 2010;341:c4372.

31. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, Walker E, Varghese S, Lao-Sirieix P, et al. Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multi-center case-control study. PLoS Med. 2015;12(1):e1001780.

32. Katz-Summercorn A, Anand S, Ingledew S, Huang Y, Roberts T, Galeano-Dalmau N, et al. Application of a multi-gene next-generation sequencing panel to a non-invasive oesophageal cell-sampling device to diagnose dysplastic Barrett's oesophagus. J Pathol Clin Res. 2017;3(4):258-67.

33. Lao-Sirieix P, Boussioutas A, Kadri SR, O'Donovan M, Debiram I, Das M, et al. Non-endoscopic screening biomarkers for Barrett's oesophagus: from microarray analysis to the clinic. Gut. 2009;58(11):1451-9.

34. Lao-Sirieix P, Rous B, O'Donovan M, Hardwick RH, Debiram I, RC. F. Non-endoscopic immunocytological screening test for Barrett's oesophagus. Gut. 2007;56(7):1033-4.

35. Pilonis ND, Killcoyne S, Tan WK, O'Donovan M, Malhotra S, Tripathi M, et al. Use of a Cytosponge biomarker panel to prioritise endoscopic Barrett's oesophagus surveillance: a cross-sectional study followed by a real-world prospective pilot. Lancet Oncol. 2022;23(2):270-8.

36. Fitzgerald RC, di Pietro M, O'Donovan M, Maroni R, Muldrew B, Debiram-Beecham I, et al. Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial. Lancet. 2020;396(10247):333-44.

37. di Pietro M. Revised British Society of Gastroenterology recommendation on the diagnosis and management of Barrett's oesophagus with low-grade dysplasia. Gut. 2018;67(2):392-3.

38. Chien S, Glen P, Penman I, Bryce G, Cruickshank N, Miller M, et al. National adoption of an oesophageal cell collection device for Barrett's oesophagus surveillance: impact on delay to investigation and pathological findings. 2023 [In press].

39. IQVIA, NHS England. NHS England Cytosponge evaluation for routine referrals: final report. 2023 [In press].

40. Januszewicz W, Tan WK, Lehovsky K, Debiram-Beecham I, Nuckcheddy T, Moist S, et al. Safety and acceptability of a non-endoscopic esophageal sampling device - Cytosponge®: a systematic review of multi-center data. Clin Gastroenterol Hepatol. 2019;17(4):647-56.e1.

41. Medicines and Healthcare Products Regulatory Agency (MHRA). Field Safety Notices (FSNs) from 5 to 9 June 2023. Medtronic: Cytosponge cell collection device. 2023 [cited 2023 Sept 04]; Available from: https://www.gov.uk/drug-device-alerts/list-of-field-safety-notices-fsns-from-5-to-9-june-2023.

42. Freeman M, Offman J, Walter FM, Sasieni P, Smith SG. Acceptability of the Cytosponge procedure for detecting Barrett's oesophagus: a qualitative study. BMJ Open. 2017;7:e013901.

43. Tan WK, Muldrew B, Khan Z, Fitzgerald RC. A crosssectional analysis of Facebook comments to study public perception of a new diagnostic test called the Cytosponge. Dis Esophagus. 2019;32(1):1-6.

44. Benaglia T, Sharples LD, Fitzgerald RC, Lyratzopoulos G. Health benefits and cost effectiveness of endoscopic and nonendoscopic cytosponge screening for Barrett's esophagus. Gastroenterol. 2013;144(1):62-73.e6.

45. Eluri S, Paterson A, Lauren BN, O'Donovan M, Bhandari P, di Pietro M, et al. Utility and cost-effectiveness of a nonendoscopic approach to Barrett's esophagus surveillance after endoscopic therapy. Clin Gastroenterol Hepatol. 2022;20(2):e51-e63.

46. Heberle CR, Omidvari AH, Ali A, Kroep S, Kong CY, Inadomi JM, et al. Cost effectiveness of screening patients with gastroesophageal reflux disease for Barrett's esophagus with a minimally invasive cell sampling device. Clin Gastroenterol Hepatol. 2017;15(9):1397-404.e7.

47. Shaw M, Cuthbertson K, Fullarton G. A health economic analysis of the introduction of a cell collection system (Cytosponge®) as a viable alternative to upper GI endoscopy in the COVID recovery. 2020 [cited 2023 Nov 30]; Available from: https://www.nss.nhs.scot/media/2997/cytosponge.pdf.

48. Swart N, Maroni R, Muldrew B, Sasieni P, Fitzgerald RC, Morris S. Economic evaluation of Cytosponge®-trefoil factor 3 for Barrett esophagus: a cost-utility analysis of randomised controlled trial data. EClinicalMedicine. 2021;37:100969.

49. Lieberman DA, De Garmo PL, Fleischer DE, Eisen GM, Helfand M. Patterns of endoscopy use in the United States. Gastroenterol. 2000;118(3):619-24.

50. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit costs of health and social care 2022 manual: technical report. 2023 [cited 2023 Sept 29]; Available from: https://kar.kent.ac.uk/100519/.

51. NHS England. National cost collection for the NHS. 2023 [cited 2023 Sept 29]; Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/.

52. Public Health Scotland. Acute hospital activity and NHS beds information (annual): year ending 31 March 2023. 2023 [cited 2023 Nov 15]; Available from: https://publichealthscotland.scot/publications/acute-hospital-activity-and-nhs-beds-information-annual/acute-hospital-activity-and-nhs-beds-information-annual-annual-year-ending-31-march-2023/.

53. Wani S, Holmberg D, Santoni G, Kauppila JH, Farkkila M, von Euler-Chelpin M, et al. Magnitude and time-trends of post-endoscopy esophageal adenocarcinoma and post-endoscopy esophageal neoplasia in a population-based cohort study: the Nordic Barrett's esophagus study. Gastroenterol. 2023;165(4):909-19.

54. Sawas T, Mazjoub AM, Haddad J, Tielleman T, Nayfeh T, Yadlapati R, et al. Magnitude and time-trend analysis of postendoscopy esophageal adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2022;20(2):e31-50.

55. Last J. A dictionary of epidemiology. 4th ed. New York: Oxford University Press; 2001.

56. Healthcare Improvement Scotland. Rapid Response: Cytosponge for the detection of pre-malignant or early curable oesophageal cancer. 2020 [cited 2023 Nov 30]; Available from: https://www.healthcareimprovementscotland.org/his/idoc.ashx?docid=4e4646d1-4582-4352-9d27-7d28ad9b4dde&version=-1.

Appendix 1: Abbreviations

+ve	positive
-ve	negative
C	circumferential length
ANIA	accelerate national innovation adoption
BEST	Barrett's oesophagus trial
BIA	budget impact analysis
CI	confidence interval
EET	endoscopic eradication therapy
EMR	endoscopic mucosal resection
GORD	gastro-oesophageal reflux disease
HCP	healthcare professional
IAPS	Inventory to Assess Patient Satisfaction
ICER	incremental cost-effectiveness ratio
IQR	inter-quartile range
MHRA	Medicines and Healthcare Products Regulatory Agency
NA	not applicable/not available
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OGD	oesophago-gastro-duodenoscopy
OR	odds ratio
PSA	probabilistic sensitivity analysis
PSSRU	Personal and Social Services Research Unit
QALY	quality adjusted life-years
RCT	randomised controlled trial
RFA	radiofrequency ablation
SD	standard deviation
SHTG	Scottish Health Technologies Group
SIMD	Scottish index of multiple deprivation

STAI-6	Spielberger State Trait Anxiety Inventory
TFF3	trefoil factor 3
TM	trademark
UK	United Kingdom
US	United States
VAS	visual analogue scale

Appendix 2: Definitions of diagnostic accuracy terms

Sensitivity: the probability that a person having a disease will be correctly identified by a clinical test, that is the number of true positive results divided by the total number with the disease[55].

Specificity: the probability that a person not having a disease will be correctly identified by a clinical test, that is the number of true negative results divided by the total number of those without the disease[55].

Receiver operating characteristic (ROC) curve: a graph used to assess the ability of a diagnostic test to discriminate between people with or without the target condition. For most diagnostic test data the ROC curve plots sensitivity against 1-specificity for different cut-off values[55]. Area under the ROC curve can be used to compare the diagnostic accuracy of tests when multiple ROC curves are plotted on the same graph.

Appendix 3: Data from NHSScotland

Table A: Demographic information for patients with chronic reflux

Outcome	Total
Number of patients	1,305
Age, mean	55
Age, SD	14
Age, median	56
Age, range	75
Age, IQR	19
Sex (female), n (percentage)	759 (58.2%)
Sex (male), n (percentage)	546 (41.8%)

Table B: Demographic information for patients with Barrett' oesophagus under surveillance

Outcome	All	High risk
Number of patients	3,745	299
Age, mean	64	67.63
Age, SD	11.20	8.59
Age, median	66	69
Age, range	70	50
Age, IQR	15	12
Sex (female), n (percentage)	1,212 (32.36%)	76 (25.42%)
Sex (male), n (percentage)	2,533 (67.64%)	223 (74.58%)

Table C: Descriptive statistics (number of days) for stages of the pathway for high risk surveillance patients

	Time period (number of days)				
Outcome	**Last surveillance endoscopy to Cytosponge™**	**Last surveillance endoscopy to treatment**	**Cytosponge™ to endoscopy (urgent cases)[a]**	**Cytosponge™ to diagnosis[b]**	**Cytosponge™ to treatment**
Total n	299	50	281	261	50
Mean	1,187.21	1,538.04	87.43	110.84	244.20
Median	1,154	1,417.50	60	85	201
SD	514.32	546.52	78.36	85.23	153.66
IQR	562.50	950.25	55	73	121.25
Range	3,624	2,614	487	492	626

Total n varied per time period as a result of unavailable data.

[a] No oesophago-gastro-duodenoscopy (OGD; patient has been referred for, but has not had an OGD) = 18.

[b] No OGD, pathology awaited (patient has had an OGD with biopsies taken but the pathology results are not back as yet at the time of analysis) = 20.

Appendix 4: Evidence tables

Studies included in the Healthcare Improvement Scotland Rapid Response (2020)[56]

Study	Population	Study objective	Key findings
Fitzgerald (2020)[36] RCT	Patients aged 50 years or older who have been prescribed acid suppressant therapy for at least 6 months in the previous year (chronic reflux) n=13,222 (n=1,654 who successfully swallowed Cytosponge™) Age range 50–99 years 46% males	Comparing Cytosponge™-TFF3 testing with usual care	Of 6,834 study participants in the intervention group, 231 (3%) had a positive Cytosponge™-TFF3 result and were referred for an endoscopy. During an average of 12 months follow up, 140 (2%) of 6,834 participants in the intervention group and 13 (<1%) of 6,388 participants in the usual care group were diagnosed with Barrett's oesophagus (absolute difference 18.3 per 1,000 person-years, 95% CI 14.8 to 21.8, rate ratio adjusted for cluster randomisation 10.6, 95% CI 6.0 to 18.8, p<0.0001). Nine (<1%) of 6,834 participants were diagnosed with dysplastic Barrett's oesophagus (n=4) or stage 1 oesophagogastric cancer (n=5) in the intervention group. No participants were diagnosed with dysplastic Barrett's oesophagus or stage 1 gastro-oesophageal cancer in the usual care group. Among 1,654 participants in the intervention group who swallowed the Cytosponge™ device successfully, 221 (13%) underwent endoscopy after testing positive for TFF3 and 131 (8%, corresponding to 59% of those having an endoscopy) were diagnosed with Barrett's oesophagus or cancer. One patient had a detachment of the Cytosponge™ from the thread requiring endoscopic removal. The most common device related side effect was a sore throat in 63 (4%) of 1,654 participants.

Freeman (2017)[42] Qualitative	Patients with GORD n=33 adults Aged 50–69 years 52% males 10 individuals were interviewed and 23 participated in four focus groups	Assessing the acceptability of the Cytosponge™ device	Three key themes emerged from the data: the anticipated physical experience, preferences for the content of information materials and comparisons with the current gold standard test (endoscopy). Overall acceptability was high, but there was initial concern about the physical experience of taking the test, including swallowing and extracting the Cytosponge™. These worries were reduced after handling the device and a video demonstration of the procedure. Knowledge of the relationship between GORD, Barrett's oesophagus and oesophageal adenocarcinoma was poor, and some suggested they would prefer not to know about the link when being offered the Cytosponge™. Participants perceived the Cytosponge™ to be more comfortable, practical and economical than endoscopy.
Iqbal (2018)[27] Systematic review	13 studies: one RCT, three cohort studies, four case-control studies and five cross-sectional studies (6 studies reported diagnostic accuracy) Participants had eosinophilic oesophagitis, gastro-oesophageal reflux or Barrett’s oesophagus n=3,788 Median age range 34–67 years	Diagnostic accuracy of Cytosponge™ for detecting oesophageal pathologies	Patient acceptability was high. If these early results are validated the Cytosponge™ represents an important advance in the detection of oesophageal pathology that could potentially decrease the burden of endoscopic oesophageal sampling.

Januszewicz (2018)[40] Systematic review	Five studies n=2,418 Majority of participants had GORD (n=1,329, 56.7 %) or Barrett's oesophagus (n=987, 40.8%) Median participant age 62 years (IQR 54 to 68)	Acceptability and safety of Cytosponge™ compared with endoscopy with or without sedation	There were two adverse events related to the device: a minor pharyngeal bleed and one case of sponge detachment (<1:2,000). The median acceptability score for the Cytosponge™ was 6.0 (IQR 5.0 to 8.0), which was higher than endoscopy without sedation (median 5.0, IQR 3.0 to 7.0; p<0.001) and lower than endoscopy with sedation (median 8.0, IQR 5.0 to 9.0; p<0.001). Nearly all patients (91.1%) successfully swallowed the Cytosponge® and most (90.1%) had a successful first attempt. Failure to swallow the device was more likely to occur in secondary care settings (OR 5.13, 95% CI 1.48 to 17.79, p<0.01).

New secondary evidence

Study	Population	Study objective	Key findings
NICE (2020)[15] Medical Innovation Briefing	People seeing their GP with heartburn or reflux symptoms needing acid suppressant medicine	Effectiveness of Cytosponge™-TFF3 testing for detection of Barrett's oesophagus	The main points from the evidence summarised in this briefing are from five studies (two systematic reviews, one RCT and two cross-sectional studies). A review of five studies showed that Cytosponge™ was significantly more acceptable compared with endoscopy. Another review of 13 studies reported a pooled sensitivity of 81% and specificity of 91% using Cytosponge™ for detecting Barrett's oesophagus.

			RCT results showed that the estimated adjusted relative risk of detecting Barrett's oesophagus was 10.6 (95% CI 6.0 to 18.8) for Cytosponge™ followed by an endoscopy compared with the standard care group that had endoscopy at 12 month follow up. Three studies reported the sponge detached from the string in a total of four people.

New observational studies

Study	Population	Study objective	Key findings
Chien (in press)[38] Cohort	n=3,223 (Cytosponge™ tests, unclear if any repeat tests) Median age 67 in year one (IQR 59 to 73) Median age 66 in year two (IQR 58 to 73) 68.3% males in year one 60.0% males in year two	To evaluate if the CytoSCOT programme has reduced delays to Barrett's surveillance and whether delayed Barrett's surveillance has negatively impacted the endoscopic pathology patterns within this patient cohort	In year one versus year two, there was a longer median delay to surveillance (9 vs. 5 months, p<0.001), an increased proportion of patients with delayed surveillance (72.6% vs. 57.0%, p<0.001) and more high risk patients (12.0% vs. 5.3%, p<0.001). 425/3,223 patients (13.2%) were further investigated with endoscopy, 57.9% of which were high risk. As surveillance delay increased beyond 24 months, high risk patients were significantly more likely to have dysplasia or malignancy (p=0.004).
IQVIA (in press)[39] Service evaluation	Data from 17 cancer alliances and 30 hospital sites across England n=1,549 patients from clinical systems n=352 patient survey responses	Three core objectives: 1. Determine the extent to which the intended outcomes of the programme were achieved, along with identifying unintended consequences.	Cytosponge™ testing effectively reduced endoscopy demand in secondary care by 78% in patients who completed a Cytosponge™ test. There is some evidence that Cytosponge™ helped to triage patients (both high and low risk), as most Barrett's oesophagus cases were found on the endoscopy outcomes of

	n=22 clinical staff interviews n=28 patient interviews	2. Support a decision on a potential national roll out. 3. Inform future NICE appraisal processes.	patients with positive test results, while no cases were detected in patients who had a negative test result but nonetheless underwent an endoscopy. Cytosponge™ patients were tested quickly following triage and waited on average three weeks to receive their test result. The effectiveness of Cytosponge ™ in reducing endoscopy demand increased over time during the pilot period. Cytosponge™ is an acceptable and safe procedure in secondary care settings, and no serious adverse events were reported during the evaluation period. Most patients (82%) were satisfied with their experience of the Cytosponge™ test, including the time they waited for the test and their results, but with some differences by sex. Most patients experienced no pain or just mild pain during or immediately after the test, with most patients experiencing some level of discomfort rather than pain. Most patients were unconcerned with the level of discomfort they experienced during the test. Cytosponge™ programme resulted in a per patient cost saving of £421.57 and a very slight decrease in QALYs of 0.0041. The 5-year net budget impact of introducing Cytosponge™ nationally depends on the proportion of patients assigned to Cytosponge™ instead of endoscopy in the first year. An initial 10% share of eligible patients assigned to Cytosponge™ in year one, with an increase of 10 percentage points every year, gives a net budget saving over 5 years of £10,297,798.

			An initial 90% share of eligible patients assigned to Cytosponge™ in year one, with an increase of 10 percentage points every year, gives a net budget saving over 5 years of £32,993,996. A change in the price of the Cytosponge™ test has a significant effect on both cost-effectiveness and budget impact. The Cytosponge™ programme is both a cost-effective and budget saving intervention.
Landy (2023)[17] Cohort	n=10,577 Patients with chronic reflux n=4,456 18.0 % aged <40 years 18.3 % aged ≥70 years 44.9 % males Patients with Barrett's oesophagus n=6,121 70.4% aged ≥60 years 7.4% aged ≥80 years 70.5% males	To evaluate the range of Cytosponge™ findings and the impact on endoscopy services	92.5% of Cytosponge™ tests (9,784/10,577) were sufficient for analysis. In the cohort of patients with reflux 14.7% had one or more positive biomarkers requiring endoscopy (TFF3 13.6%, p53 0.5%, atypia 1.5%). Among samples from individuals undergoing Barrett's surveillance, TFF3 positivity increased with segment length (OR 1.37 per cm, 95% CI 1.33 to 1.41, p<0.001). Some surveillance referrals (21.5%) had <1 cm segment length, of which 65.9% were TFF3 negative. Of all surveillance procedures, 8.3% had dysplastic biomarkers (4.0% for p53 and 7.6 % for atypia), increasing to 11.8% in TFF3 positive cases with confirmed intestinal metaplasia and 19.7% in ultra long segments.
Pilonis (2022)[35] Cross-sectional and prospective cohort	Participants with Barrett's oesophagus undergoing surveillance endoscopy Training cohort n=557 Median age 65 (IQR 59–72) 81% males Validation cohort	Derive and evaluate Cytosponge™ biomarkers and clinical risk factors to triage patients at high, moderate and low risk of oesophageal cancer	The prevalence of high grade dysplasia or cancer determined by the current gold standard of endoscopic biopsy was 17% (92/557 patients) in the training cohort and 10% (35/344) in the validation cohort. From the new biomarker analysis, the risk of high grade dysplasia or intramucosal cancer in the high risk group was 52% (68/132) in the training cohort and 41% (31/75) in the validation cohort, compared with 2% (5/210) and 1% (2/185) in the low risk group, respectively.

	n=334 Median age 67 (IQR 58–73) 75% males Prospective cohort n=223 Median age 69 (IQR 60–74) 74% males		In the real world setting, Cytosponge™ results prospectively identified 39 (17%) of 223 patients as high risk (atypia or p53 overexpression, or both) requiring endoscopy, among whom the positive predictive value was 31% (12/39) for high grade dysplasia or intramucosal cancer and 44% (17/39) for any grade of dysplasia.

Patient aspects

Study	Population	Study objective	Key findings
Ghimire (2023)[22] Cohort study nested in an RCT	Participants with GORD who answered 15 or more questions from the IAPS survey in an RCT n=1,458 48% males Aged >50 years	To explore factors associated with the worst experiences of Cytosponge™ testing	The majority of respondents had a positive experience, with an overall median IAPS score of 1.7 (IQR 1.5 to 2.1). High (OR 3.01, 95% CI 2.03 to 4.46, p<0.001) or very high (OR 4.56, 95% CI 2.71 to 7.66, p<0.001) anxiety (relative to low or normal anxiety) and a failed swallow at the first attempt (OR 3.37, 95% CI 2.14 to 5.30, p<0.001) were highly significant predictors of the least positive patient experience in multivariable analyses. Sex (p=0.036), height (p=0.032), alcohol intake (p=0.011) and education level (p=0.036) were identified as statistically significant predictors.
Maroni (2022)[21] Mixed methods study within an RCT	Patients with chronic reflux who were participating in the BEST3 RCT n=1,750 Age range 50 to 99 years 47% males	To understand patient experiences of the Cytosponge™ test through survey results and interviews	1,488 patients successfully swallowing the Cytosponge™ completed the follow-up questionnaires. 30 patients were interviewed, including four with an unsuccessful swallow. Overall, participants were satisfied with the Cytosponge™ test. Several items showed positive ratings, in particular convenience and accessibility, staff's interpersonal skills and perceived technical competence.

			The most discomfort was reported during the Cytosponge™ removal, with more than 60% of participants experiencing gagging. Nevertheless, about 80% were willing to have the procedure again or to recommend it to friends, even participants experiencing discomfort. Median anxiety scores were below the predefined level of clinically significant anxiety and slightly decreased between baseline and follow up ($p<0.001$). Interviews revealed concerns around the ability to swallow, participating in a clinical trial, and waiting for test results.
Tan (2019)[43] Cross-sectional	n=2,837 Facebook users	Analysis of comments posted on Facebook in response to a video demonstrating the Cytosponge™ test	The video received 22.5 million views and 2,837 comments within 4 months. Of these, 525 comments were positive, 215 were unknown, 179 were negative, 71 were questions, and 1,847 were tagged comments. Among positive comments, recurrent themes were that it was innovative, could lead to early cancer detection, and more favourable than endoscopy. Among negative comments, a recurring theme was concern about the risk of gagging and vomiting. Among questions, a recurring theme was related to the risk of Cytosponge™ detachment.