

Clinical guide for using capsule sponge tests in the upper GI Barrett's surveillance pathway

Scope

A capsule sponge test is a non-endoscopic test that involves the collection of oesophageal cells for cytopathology and immunostaining. This is a swallowable cell collection sponge, contained within a capsule, with an attached string/thread. The capsule is ingested by the patient and dissolves in the stomach, at which point the internal sponge starts to expand. After approximately 7 minutes, the sponge will have fully expanded and is then retrieved using the attached string; as the sponge is retrieved, cells are collected from the lining of the oesophagus and the sponge is sent for laboratory testing to detect Barrett's oesophagus.

Cytosponge™ is a capsule sponge test that was developed by Medtronic. It consists of a tethered sponge in a capsule that is swallowed and when brought up, it collects oesophageal cells.

EndoSign® is a capsule sponge test that was developed by Cytel in 2023. It works in the same way as Medtronic's Cytosponge™ device, with the addition of an applicator. The EndoSign® device applicator is designed to hold a pre-bunched thread that allows the user to deposit the capsule and pre-bunched thread onto the patient's mouth. The applicator is held externally by the patient during the procedure.

Samples collected using the abovementioned cell collection devices are further assessed for diagnosis of intestinal metaplasia (TFF3) and dysplasia (atypia and p53).

During the Covid-19 pandemic, endoscopy waiting lists increased significantly in the NHS in England. Although the majority of these people will not have cancer or other serious pathology, this guidance details how Cytosponge™ and EndoSign® capsule sponge tests can be used to prioritise access to upper GI endoscopy for patients with diagnosed Barrett's Oesophagus undergoing surveillance who are therefore at an increased risk of cancer. Identifying those patients with likely dysplasia and cancer will support services to prioritise patients who are most at risk of serious pathology for endoscopy and treatment, whilst minimising the number

of upper GI endoscopy procedures required for those at low risk for whom endoscopy can be delayed or in some cases avoided.

This document provides guidance for the use of Cytosponge™ and EndoSign® in the upper GI endoscopy pathway for patients with diagnosed Barrett's Oesophagus on routine surveillance to triage patients into low, moderate, or high risk of oesophageal cancer.

Pathological assessment of the Cytosponge™ and EndoSign® samples will be carried out centrally by the company Cytel. Details of this are included in this guidance.

The NHS Cancer Programme, in collaboration with Cancer Alliances and NHS Trusts, have established capsule sponge test clinics to test and develop the evidence base for this technology in different patient populations, in addition to supporting the restoration of endoscopy services during the Covid-19 pandemic. Separate guidance is available for the use of capsule sponge tests for patients on a routine referral for endoscopy with acid reflux symptoms. Cytosponge™ was introduced at the start of the pilot as the only available product on the market. EndoSign® is a newly available device that can be used in place of Cytosponge™.

Clinical evidence and data on Cytosponge™ and EndoSign®

As the cell collection methodology is the same for both Cytosponge™ and EndoSign®, the pivotal evidence base is derived from the Cytosponge™ device. Cytosponge™ is a CE marked device that has been used in research studies since 2015 and there are several publications showing the clinical evidence summarised below. EndoSign® is a UKCA and CE marked device available commercially since June 2023. Both devices utilise identical biomarker tests carried out by Cytel.

- There have been three clinical trials that demonstrate the safety, acceptability and diagnostic accuracy of Cytosponge™ to detect Barrett's Oesophagus. There are some evidence gaps for its use in secondary care, but the evidence has been deemed strong enough by the NHS Cancer Programme's Expert Advisory Group for Innovation and the Clinical Advisory Group for a pilot roll-out. The evidence gaps will be addressed through the evaluation.
- Applicability to secondary care: the feasibility study BEST1 was conducted in 504 patients in 11 general practices [PMID: 20833740], accuracy study BEST2 performed in secondary care in >1,400 patients [PMID: 25634542] and the randomised study

BEST3 involved >1,650 Cytosponges™ administered in 72 GP surgeries [Gastro 2019,156;S284 & PMID: 30075763]. Data from the control arm of BEST2 support the use of Cytosponge™ in secondary care, however the data is not randomised [PMID: 25634542].

- Safety: Cytosponge™ administration is very safe [PMIDs: 19651633, 20833740, 25634542, 17566045, Gastro 2015, 148(4);S16]. The detachment rate is currently quoted at <1:5,000 with easy retrieval at endoscopy. The commonest side-effect is sore throat which resolves within a few days. It avoids the risks associated with sedation in endoscopy and many patients prefer the convenience and speed of this test compared with endoscopy. Furthermore, it can be delivered in a more Covid-secure environment.
- Acceptability: The Cytosponge™ procedure scored a median score of 6.0 (95%CI 5.0-8.0) on a visual analogue scale from 0 (worst experience) to 10 (best experience), which is higher than endoscopy [PMIDs: 19651633, 20833740, 25634542, 17566045, Gastro 2015, 148(4);S16] and 8.6/10 in the recently completed BEST3 study [Gastro 2019,156;S284].
- Cytosponge™: TFF3 test is accurate for diagnosing Barrett's Oesophagus with a sensitivity of approximately 80% (intention to treat analysis) and specificity of >92%. When patients are recalled if the sample is inadequate (12-15%) the sensitivity is 94% (PMID: 25634542).
- Cytosponge™ can also diagnose other clinically relevant oesophageal conditions including early cancer, eosinophilic Oesophagitis (EoE), oesophageal candida, oesophagitis, and *H.pylori*, if present in the proximal stomach.
- A TFF3 positive Cytosponge™ indicates intestinal metaplasia (IM) - this is often from Barrett's but can also arise from IM of the gastric cardia which can indicate more extensive gastric IM, a premalignant condition. In the BEST3 study this has led to an early diagnosis of gastric cancer in one case.
- Cost-effectiveness: A full health economic analysis is underway for BEST3 (PMID: [34195582](#)) and cost effectiveness and value for money will be looked at as part of the evaluation of this pilot.

- EndoSign® has undergone performance and safety testing. Performance verification studies carried out in volunteers has shown 100% sufficient cellularity for diagnosis. In addition, an independent mechanical safety testing has demonstrated an equivalent or higher Process Capability Index (Cpk) value, indicating equivalent or lower detachment per million devices compared to Cytosponge™. The detachment rate for EndoSign® is estimated to be less than 0.01 in 1,000,000.

Target population and exclusions

This guidance is specific for the use of Cytosponge™ and EndoSign® in patients who have diagnosed Barrett's Oesophagus and are undergoing routine surveillance with no alarm symptoms.

Inclusion criteria for Cytosponge™ and EndoSign®:

Patients with a confirmed Barrett's Oesophagus diagnosis who has had a full set of biopsies using Seattle protocol (often this will be on a dedicated surveillance list which is preferable for a long segment) who are due to have their next surveillance procedure.

Exclusion criteria for Cytosponge™ and EndoSign® (absolute contraindications):

- **Alarm symptoms:**
 - **dysphagia**
 - **dyspepsia and weight loss**
 - **dyspepsia and anaemia**
- Patient with indefinite dysplasia or low-grade dysplasia on last endoscopy who has not had treatment. Please note, not excluded if patient has indefinite dysplasia or low-grade dysplasia prior to last endoscopy
- Previous cancer of the oesophagus
- Patient with a diagnosis of an oropharyngeal, oesophageal or gastro-oesophageal tumour
- Patient who has had treatment to the oesophagus e.g. photo dynamic therapy, endoscopic mucosal resection, radio frequency ablation, surgery
- Patient known to have oesophageal varices or cirrhosis of the liver
- Patient with a known anomaly of the oesophagus e.g. webbing, pouch, stricture etc.
- Patients unable to give consent
- Patients who have had a stroke or any other neurological disorder where their swallowing has been affected

- Patients who have had a myocardial infarction in the last 3 months.
- Patients who have had fundoplication

Triaging process

A Dyspepsia Nurse or Gastroenterologist will identify appropriate patients who are due to have an upper GI endoscopy as part of their routine Barrett's surveillance. A letter should be sent, or a telephone call should be carried out to offer Cytosponge™ or EndoSign® to the patient as an alternative to endoscopy. Patients should be provided with a patient leaflet (paper or online).

Preprocedural preparation

Patients should be advised to be nil by mouth 4 hours prior to the appointment for the Cytosponge™ or EndoSign® test. For patients on anticoagulant medication, specific instructions should be provided.

Anticoagulation

For patients on anticoagulation therapy, please follow the appropriate guidance below, which aligns to the BSG guidance on low risk endoscopy procedures. Please note, this guidance is different to the practice carried out in the BEST trials.

P2Y12 Receptor Antagonist Antiplatelet Agents e.g. Clopidogrel, Prasugrel, Ticagrelor

- Continue therapy

Direct Oral Anticoagulants e.g. Dabigatran, Rivaroxaban, Apixaban, Edoxaban

- Omit DOAC on morning of procedure

Warfarin

- Continue warfarin
- Check INR during the week before endoscopy
 - If INR within therapeutic range, continue daily dose
 - If INR above therapeutic range (above 3.5), escalate to their responsible physician and reduce daily dose until INR returns to therapeutic range

Consent

This should be undertaken in the same way as consent is obtained for upper GI endoscopy i.e. the completion of an NHS Consent Form 1 and retained in the patient notes. The patient should be asked if they are willing for their anonymised sample and data to be used for research, if so, the research box should be ticked. Ticking this box is essential for the data to be included as part of the evaluation.

Procedure

The Cytosponge™ or EndoSign® may be performed by a trained nurse or healthcare professional that has been assessed and deemed competent to carry out the procedure independently (see below for training requirements).

Before the procedure please check whether the patient has any swallowing difficulties. If the patient has any dysphagia, they are not eligible for Cytosponge™ or EndoSign® and an endoscopy should be carried out.

Before using a Cytosponge™ or EndoSign®, the device should be inspected, and the expiration date should be checked. Do not use the device if it is damaged or it has expired. If a device looks damaged, such as visible cracks in the capsule or protrusion of the sponge through the capsule, it should be reported to the relevant company.

The patient is asked to sit in a chair and swallow the Cytosponge™ or EndoSign® capsule and string together with some water. For the Cytosponge™ device, the end of the string is attached to a piece of card which the nurse will hold (figure 1). For the EndoSign®, the string is pre-bunched in an applicator that the patient will hold (figure 2). The capsule will be in the patient's stomach for around 7½ minutes until it dissolves completely, releasing the sponge inside the stomach. The nurse will then remove the sponge from the patient's stomach and up through the oesophagus by pulling quickly and gently on the string taking about 1-2 seconds. The patient has the option to have a local anaesthetic spray into their throat before the sponge is removed.

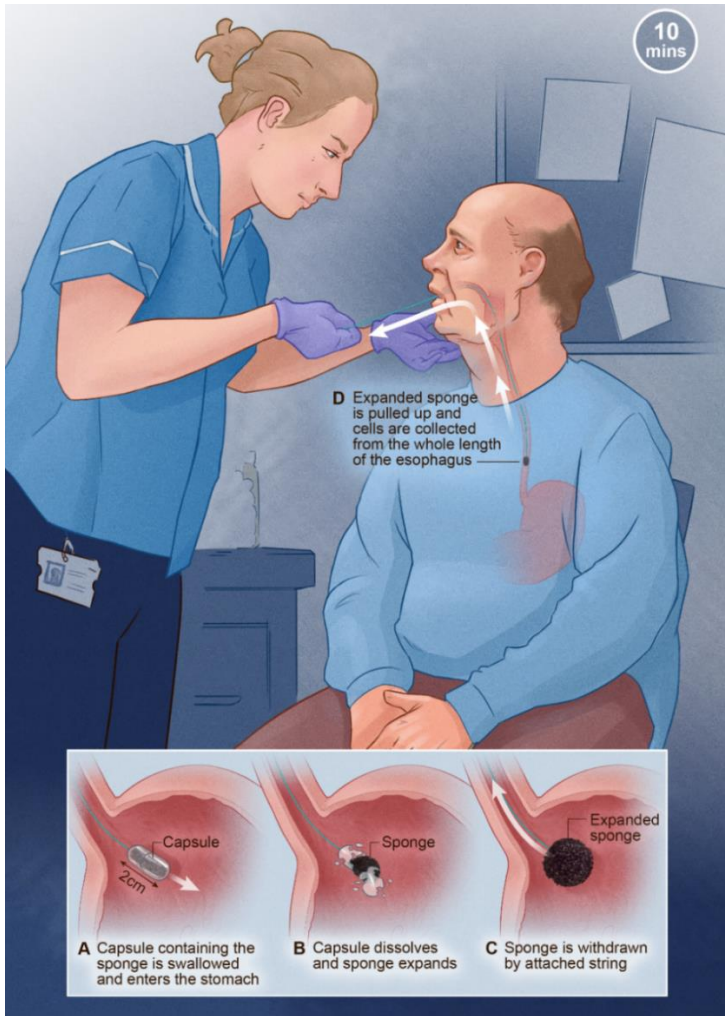


Figure 1: Administration and passage of the Cytosponge™ device to obtain a sample of oesophageal epithelial cells. Drawn by Campbell Medical Illustration (Glasgow, Scotland)

EndoSign® capsule sponge device

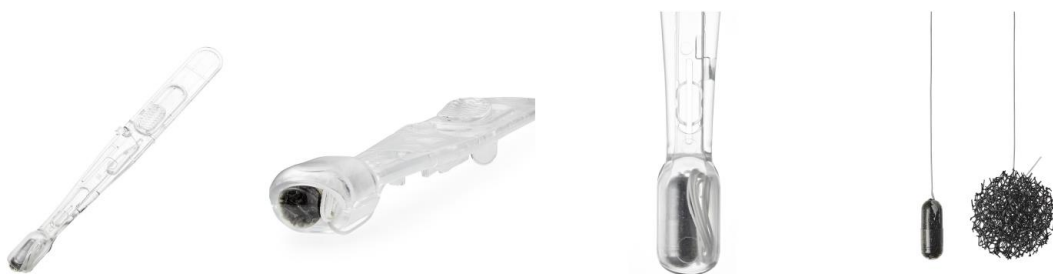


Figure 2: EndoSign® capsule sponge device – applicator and sponge. Image produced by Cytel.

Please note the following factors when you withdraw the sponge:

- **Blood.** If there is any blood on the sponge this could indicate severe inflammation or cancer. The patient should be referred for endoscopy as urgent two-week wait.
- **Lax string.** You should feel some tension when you withdraw the sponge even if there is a hiatus hernia. A lax string on withdrawal is usually from a poor swallow. Please note this on the Cytel request form. When a lax string is noticed in a Barrett's patient, it may be possible that the pathology result is TFF3+, but the sponge did not sample the entire Barrett's segment (particularly when the segment length is >6cm), so an endoscopy should be considered.

The sponge is then placed in a sample collection kit provided by Cytel and secured with a patient identification label which includes the hospital number, year of birth and sex of the patient. The sample collection kit is accompanied by a patient requisition/request form which should be completed during the clinic.

It is important that the request form has important information to assist the pathologist including:

- the length of the Barrett's segment (Prague length)
- any previous dysplasia history
- whether you noted a lax string on withdrawal or any blood on the sponge

Patient specimens and requisition forms are shipped using a secure courier network to Cytel who will carry out the pathological assessment. Diagnostic results are shared with the requesting clinician using NHS.net emails or an electronic reporting connector within 14 working days from the day of sample receipt in the lab.

In the rare event that the Cytosponge™ or EndoSign® detaches and is retained in the stomach, urgent upper GI endoscopy and removal of Cytosponge™ or EndoSign® must be performed. Please follow local guidance and pathways for removal of foreign body.

In the extremely unlikely event that there is inhalation of the Cytosponge™ or EndoSign® (never happened to date), urgent consultation with interventional respiratory or cardiothoracic teams is required and urgent bronchoscopy will be required.

Discharge and safety netting

Following the procedure, the patient will be given instructions regarding follow up arrangements and who to contact if there is a query or problem post procedure. The patient will be advised that the results will be available in approximately 2-3 weeks' time, and this will be communicated by letter and/or telephone by the hospital trust. The report received from Cytod must be formally uploaded onto the patient records. The hospital trust is also responsible for informing the GP or referring clinician via letter of the patient outcome and what follow-up plan has been arranged.

Common symptoms post procedure

The most common side effect of the procedure is a sore throat, and this can be treated with appropriate conservative measures or simple analgesia. Mild abdominal pain and nausea may also be experienced.

Symptoms post procedure that require urgent clinical review

Symptoms such as black stool, significant chest pain, severe throat pain, persistent difficulty swallowing, abdominal pain and difficulty breathing require urgent assessment. If a patient develops these symptoms immediately following the procedure, an assessment should be made urgently by the most senior physician. If a patient develops these symptoms following discharge at home, they should be advised to seek urgent medical attention in their local Accident and Emergency department.

Further follow up will be organised for the patient according to the results (see figure 2). Please correlate results with clinical symptoms and manage accordingly.

Cytopathology results

Patients will be classified by the managing clinician into low, moderate, or high-risk depending on the Cytosponge™ or EndoSign® results and their clinical risk factors (age, sex, and segment length). An assessment of clinical risk factors will help to safety net patients and minimise the risk of missing dysplasia.

Cytopathology results

- Atypia (definite or of uncertain significance) and/or abnormal or equivocal p53 = high risk. Patient requires endoscopy as urgent two-week wait.
- No atypia, normal P53, but has clinical risk factors = moderate risk. Patient requires endoscopic assessment at 12-18 months. These clinical risk factors are: an ultra-long segment (M>10 or 238 C>6) OR patients with a long-segment (M>5 or C≥3) AND either male or age>60 years.
- No atypia, normal P53 and no clinical risk factors = low risk. Patient requires repeat Cytosponge or endoscopy at an interval determined by the BSG guidance.

TFF3

- TFF3 negative, normal P53, no atypia = low risk. There may be patients on Barrett's surveillance that are TFF3 negative because they have gastric metaplasia only or a short segment with only focal IM. Clinical judgement based on previous endoscopy and biopsy results should be used to either put them into the low risk category or discharge them according to BSG guidance.

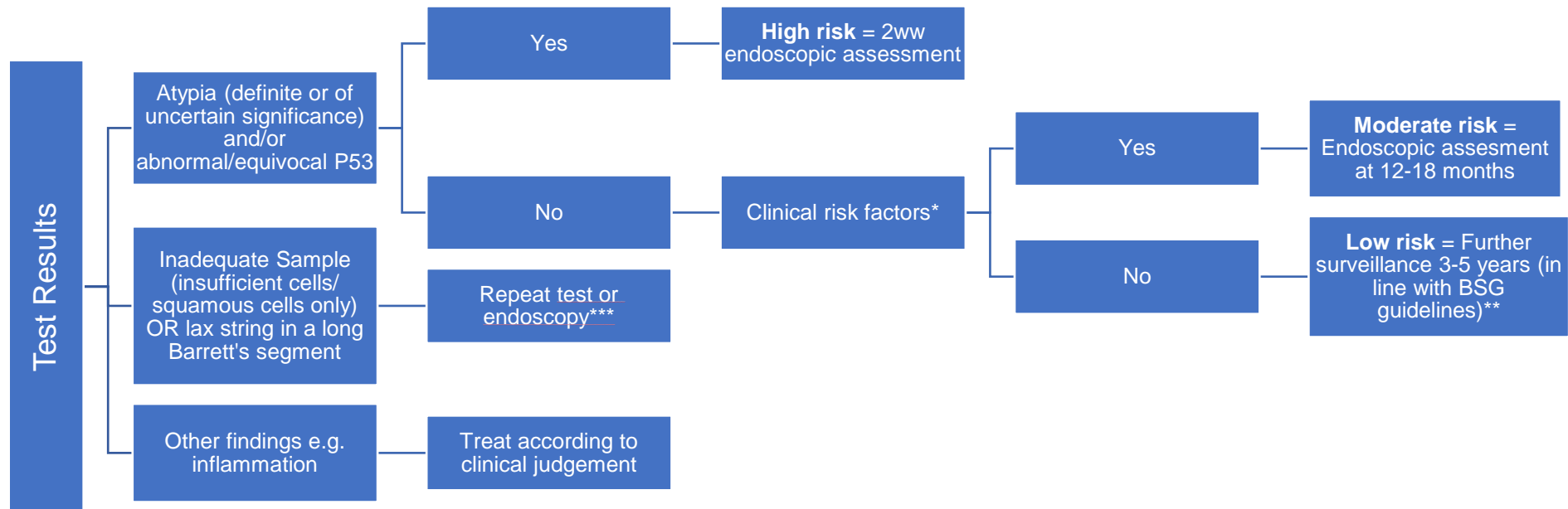
Inadequate samples

- Insufficient sample: Patient requires repeat Cytosponge™ or EndoSign® testing or an endoscopy within 3 months.
- Squamous cells only, no atypia: This suggests that the device did not reach the stomach and so the Barrett's segment has not been sampled. Patient requires repeat Cytosponge™ or EndoSign® testing or an endoscopy.
- **Remember** that if the segment is long (>6cm) and there was a **lax string** on withdrawal this means the Barrett's segment sampling may not have been complete and an endoscopy is recommended even if TFF3+ cells are seen on the Cytosponge™ or EndoSign®.

Other findings

- Other benign diagnoses/findings e.g. inflammation, candida etc. Patient treated according to clinical judgement

Figure 2: Follow up required for Cytosponge™ or EndoSign® sample results



*Clinical risk factors:

1. Ultra-long segment (M>10 or C>6) **OR**
2. Patients with a long segment (M>5 or C≥3) **AND** either male or age>60 years

** If TFF3 negative, no Intestinal Metaplasia has been picked up from the Cytosponge™ or EndoSign®. This patient may have gastric metaplasia only or focal IM only. Clinical judgement based on previous endoscopy and biopsy results should be used to consider discharge or manage according to low risk.

***NB Please consider patient's symptoms and escalate to endoscopy/urgent endoscopy if concerning

Training for Cytosponge™

Training will be organised nationally and delivered locally on a one-to-one basis in individual hospital trusts. Clinical leads in each pilot clinic are responsible for ensuring nurses (band 7+ or band 6 if supported by band 7+) with sufficient experience are nominated to undertake training. Training may be completed within one clinic session with 8-10 patients for new nurses with no prior experience of capsule sponge testing.

All staff delivering Cytosponge™ procedures must have completed and passed the training and competency assessment.

Training for EndoSign®

Training will be organised by Cytel and delivered locally on a one-to-one basis in individual hospital trusts. Clinical leads in each pilot clinic are responsible for ensuring nurses (band 7+ or band 6 if supported by band 7+) with sufficient experience are nominated to undertake training. Training may be completed within one clinic session with 8-10 patients for new nurses with no prior experience of capsule sponge testing.

For nurses with prior experience in delivering capsule sponge services, a transition training will be carried out to ensure training on the new device is delivered. Training will be completed within one clinic session with 3-5 patients for transitioning nurses.

All staff delivering EndoSign® procedures must have completed and passed the training and competency assessment.

Evaluation

Trusts were asked to collect a minimum dataset for each procedure including patient outcomes, which will feed into an evaluation (possibly DELTA¹) to understand the impact of Cytosponge™ and/or EndoSign® on endoscopy demand. More information on sharing the collected data will be provided to Trusts. There are no further data collection requirements for this evaluation and Trusts should use OPCS-4 and SNOMED codes to capture patients who receive a Cytosponge™ or EndoSign®.

¹ Project DELTA is funded by Innovate UK and aims to implement and evaluate Cytosponge in secondary care for Barrett's surveillance patients