Final Report

NHS England Cytosponge Evaluation for Routine Referrals

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IQVIA

NHS England

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ABBREVIATIONS

ABBREVIATIONS	DESCRIPTION
BI	Budget impact
BIM	Budget impact model
BO	Barrett's oesophagus
CEM	Cost-effectiveness model
CEAC	Cost-effectiveness acceptability curve
CG	Clinical guidance
CI	Confidence interval
CMA	Cost-minimisation analysis
DAP	Diagnostic assessment programme
DSA	Data sharing agreement
FTE	Full time equivalent
GBP	Great British Pound
GI	Gastrointestinal
GORD	Gastro-oesophageal reflux disease
GP	General practitioner
HCP	Healthcare professional
HGD	High-grade dysplasia
HRG	Healthcare resource group
IQR	Interquartile range
IMD	Indices of multiple deprivation
ICS	Integrated care system
KOL	Key opinion leader
LGD	Low-grade dysplasia
LY	Life year
MAP	Model analysis plan
MI	Management information (data)
MIB	MedTech Innovation Briefing
NDBO	Non-dysplastic Barrett's oesophagus
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
OAC	Oesophageal adenocarcinoma
OC	Oesophageal cancer
ONS	Office for National Statistics
OWSA	One way sensitivity analysis
PS	Propensity score
PSA	Probabilistic sensitivity analysis
P53	Tumour protein p53 gene
QALY	Quality-adjusted life year
SAP	Statistical analysis plan
SD	Standard deviation
TFF3	Trefoil factor 3
WWC	World with Cytosponge
WWoC	World without Cytosponge
WTP	Willingness to pay
2WW	2 week wait

EXECUTIVE SUMMARY

Context

Gastro-oesophageal reflux is a relatively common condition, with approximately 10 – 20% of the population experiencing some degree of symptoms, some of whom may already have or will develop Barrett's oesophagus (BO), a precursor to oesophageal cancer (OC) (El-Serag et al., 2014). A variety of demographic and lifestyle factors may increase the risk of gastro-oesophageal reflux, including older age, male sex, intake of analgesics, consumption of certain types of food and drinks, smoking, high body mass index, and limited physical activity (Yamasaki et al., 2018).

BO is currently diagnosed via endoscopy following a General Practitioner (GP) referral to a gastroenterologist or other specialist in secondary care. However, the COVID-19 crisis disrupted elective care services leading to longer patient waiting times for endoscopy.

The National Health Service (NHS) Long Term Plan sets out aims to improve cancer outcomes through early diagnosis and treatment. Cytosponge was introduced by NHS England (NHSE) as a triaging tool in secondary care for patients with low-risk reflux symptoms, aiming to reduce the waiting times for endoscopy and ensure patients at higher risk of cancer could be prioritised.

Cytosponge pilot programme

Cytosponge is a capsule sponge test – 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. It can be used to help triage BO through assessing intestinal metaplasia (TFF3) and dysplasia (atypia and p53).

When used as a triaging tool in secondary care, an expected benefit of Cytosponge for patients with low-risk reflux symptoms is that it reduces the number of onward referrals for an endoscopy. This presents a potential means of accelerating the recovery of elective care services post COVID-19 and may support the ambitions set out in the NHS Long Term Plan.

In January 2021, **NHSE launched a pilot of the Cytosponge tool for triaging patients with low-risk reflux symptoms on a routine referral pathway in the secondary care setting**. For the pilot, eligible patients waiting for a routine endoscopy on the standard diagnostic pathway were offered a Cytosponge test as an alternative to their endoscopy. Patients that accepted the offer were subsequently removed from the endoscopy pathway and placed on an alternative Cytosponge pathway. Note that high-risk patients or those displaying alarm symptoms (such as dysphagia, dyspepsia with weight loss or anaemia) were not included in this pilot and were on an urgent clinical pathway.

The pilot was launched across 17 Cancer Alliances and 30 hospital sites across England. The **intended outcomes of the pilot** were to:

- Reduce overall healthcare resource use and associated costs by replacing some endoscopies with a Cytosponge test.
- Reduce overall waiting times/waiting lists (demand) for endoscopy.
- Improve clinical outcomes.

- Improve patient experiences.
- Reduce health-related inequalities.

Evaluation objectives and design

Following the start of the pilot, **an evaluation was also undertaken,** running alongside the pilot. The evaluation ran from August 2021 (design and strategy development) until August 2023 (final reporting), and used data collected from patients seen between February 2021 and March 2022. The evaluation aimed to address evidence gaps specific to the use case within the secondary setting and had **three core objectives**:

1. Determine the extent to which the intended outcomes of the programme were achieved, along with identifying unintended consequences.
2. Support a decision on a potential national roll-out.
3. Inform future National Institute of Health and Care Excellence (NICE) appraisal processes.

The evaluation was framed around seven key evaluation questions:

1. What impact does Cytosponge (delivered in secondary care as a routine referral triaging tool) have on endoscopy demand?
2. What impact does Cytosponge have on patient outcomes?
3. What impact does Cytosponge have on the diagnostic experience of patients?
4. How does Cytosponge affect patient inequalities, both in access to a diagnosis, and in outcomes?
5. What are the enablers and barriers to the implementation of Cytosponge in secondary care?
6. What is the cost-effectiveness and budget impact of Cytosponge when used as a diagnostic triage tool in secondary care?
7. What resources would be required for a national roll-out of this programme?

Data was gathered using a range of methodologies (e.g., surveys, semi-structured interviews, workshops, review and analysis of primary and secondary data sources, econometric analysis) **through four workstreams**:

- **Process Evaluation** workstream to understand the enablers, barriers, sustainability and scalability of the Cytosponge diagnostic pathway.
- **Patient Experience Evaluation** workstream to understand the experience of patients as reported by patients themselves.
- **Impact Evaluation** workstream to understand the impact of the pilot programme on clinical and patient outcomes and hospital resource use.
- **Health Economics Evaluation** workstream to quantify the net cost impact of Cytosponge on budgets and its cost-effectiveness.

Each evaluation question was explored using data and analysis by one or more workstreams. For evaluation questions assessed using data from more than one workstream, individual workstream findings were compared, triangulated and aligned against each other to arrive at a holistic analysis. In some cases, sample sizes were too small to provide conclusive findings (e.g., when disaggregating by ethnicity) but some possible differences / trends etc., could still be observed in areas of interest. Any relevant caveats, assumptions or explanations are provided in the text in these cases.

Evaluation findings

Impact of Cytosponge on endoscopy demand

Cytosponge testing was very effective in reducing endoscopy demand in secondary care, with 78% of those who completed a Cytosponge test subsequently discharged. At the same time, Cytosponge testing identified 22% of patients as being at higher risk of BO, enabling them to be referred on for an endoscopy.

There is **some evidence that Cytosponge helped to triage patients (both at low and high BO risk).** Cytosponge could be an effective triaging tool based on endoscopy outcomes of those with a negative Cytosponge test (no cases of BO were detected in patients who had a negative Cytosponge and endoscopy). Furthermore, most cases of BO were detected amongst patients who had a positive Cytosponge and received a confirmatory endoscopy. However, more research is required to determine its effectiveness by following up on all patients who received a negative test and monitoring whether any of these patients have re-presented to secondary care beyond the timeframe of this evaluation.

The recommended diagnostic pathway for endoscopy referral was followed for most patients. There were some variations in how the diagnostic pathway was followed within hospital sites – e.g., some patients tested negative following a Cytosponge test but were still referred for an onward endoscopy. These occurred as a result of both differences in clinical judgement and/or a lack of confidence amongst clinicians in test accuracy. However, these **variations in diagnostic pathway affected a small proportion of patients and had a small impact on the effectiveness of Cytosponge in reducing endoscopy demand**.

The **effectiveness of Cytosponge in reducing endoscopy demand increased over time**, with two potential reasons: a) increasing clinician confidence; and/or, b) differences in the risk profile of patients in early versus late triage time periods. The **impact of Cytosponge on overall patient waiting lists and waiting times for an endoscopy is unclear.** There is some evidence that patients might have received endoscopies more quickly due to Cytosponge effectively removing patients from the waiting list. However, within a context of declining endoscopy waiting times across the whole NHS in England during the time period of the pilot, the reductions in numbers of patients waiting more than six weeks at Cytosponge pilot sites may not have occurred solely because of the implementation of Cytosponge.

Impact of Cytosponge on patient outcomes

Patient outcomes in this evaluation refer to diagnostic outcomes (i.e., diagnosis of BO), waiting times to various points along the patient diagnostic pathway (i.e., triage or diagnosis), and acceptability and safety of the Cytosponge test. It does not refer to longer term health outcomes in relation to BO or OC.

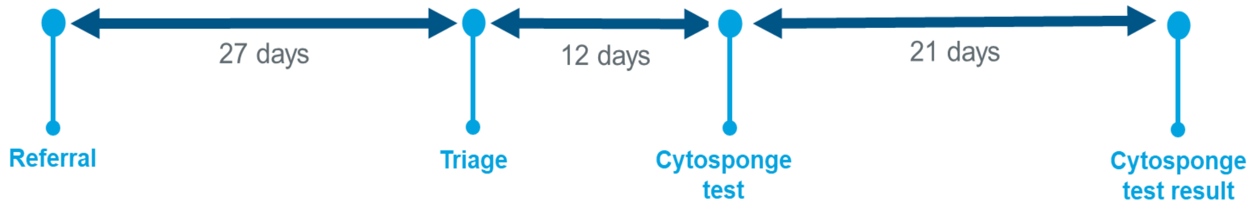
Cytosponge patients were appropriately prioritised through the diagnostic pathway based on their test result and urgency for endoscopy. Cytosponge patients with positive test results were more likely to be referred urgently for an endoscopy compared to those with uncertain or negative results. Cytosponge patients with positive results who were referred for and completed their endoscopy had the highest prevalence of BO at 27.2%, compared to only 3.5% of patients with uncertain results who completed an endoscopy and zero patients with negative results.

There is evidence that Cytosponge can triage patients accurately and is unlikely to miss BO diagnoses compared to endoscopy alone. The observed prevalence of BO was 1.8% amongst patients completing the Cytosponge test, rising to 11.2% in those referred for and completing an endoscopy. The estimated prevalence of BO in patients with gastro-oesophageal reflux symptoms varies significantly across the literature from 1-2% in a recent study in primary care (Fitzgerald et al., 2020), broadly comparable to the overall estimate observed in this pilot, to 3-9% across other studies with different patient groups across western countries (Leonardo Henry Eusebi et al., 2021; Marques de Sá et al., 2020; Qumseya et al., 2019). However, these prevalence estimates may not be directly comparable due to differences in patient selection and outcome ascertainment. Other endoscopy outcomes reported by sites included inflammation (8.5%), intestinal metaplasia (3.6%), ulcer (1.4%), oesophagitis (5.4%), and hiatus hernia (13.0%), although note that sites were instructed to report the most severe outcome observed of these non-BO outcomes, so the prevalence of less severe outcomes may be underestimated.

The prevalence of BO diagnosis was descriptively higher in Cytosponge patients (2.0%) than in the counterfactual group (1.4%), representing a relative difference of around 40%. This provides further **evidence that the risk of missed BO diagnosis associated with Cytosponge is low**. However, it should be noted that since few patients were identified as having BO in both groups, the difference between the Cytosponge and counterfactual groups was not statistically different.

On average, the total time from referral to Cytosponge test result was 60 days for all patients. This can be broken down by four key timepoints: referral, triage, Cytosponge test, Cytosponge test result. Waiting times from referral to triage (average of 27 days) were expected to be relatively long in the pilot due to sites prioritising patients who had been on the waiting list for endoscopy the longest. However, **median waiting times from triage to Cytosponge test were relatively short** (12 days) and **following the Cytosponge test, patients waited an average of 21 days to receive their test results** (Figure 1).

Figure 1. Median time from endoscopy referral to Cytosponge test result



Note: Results based on the unweighted Cytosponge cohort.

In most cases, Cytosponge lengthened the time for patients to reach the end of their diagnostic pathway (defined as the latest of their date of endoscopy or date of a negative Cytosponge test result). Cytosponge patients waited on average 75 days from referral to the end of their diagnostic pathway compared to an average 46 days for counterfactual patients. **In particular, this was the case for those receiving a non-urgent endoscopy referral following their Cytosponge test**, with average waiting times of 117 days for those referred for a routine endoscopy and 71 days for those referred for an urgent endoscopy.

Patients who received a Cytosponge test waited similar times to receive a BO diagnosis compared to counterfactual patients. Although the number of patients who received a BO diagnosis was small in both groups, there was no evidence of a difference in the time taken to receive a BO diagnosis during follow-up. All other Cytosponge patients, however, were more likely to wait longer than counterfactual patients to be discharged or receive their endoscopy result.

Cytosponge patients with a negative test result who were subsequently discharged also on average waited longer (63 days) to exit the diagnostic pathway. This was due to the targeting approach of prioritising those who had already been waiting the longest (see below) and the three-week turnaround time for results. However, the proportion of patients waiting longer than 60 or 90 days was lower for Cytosponge patients (12% and 4%, respectively) compared to counterfactual patients (24% and 18%, respectively). This indicates that although most Cytosponge patients waited longer to reach the end of their diagnostic pathway, those **patients who had a negative result and were subsequently discharged were more likely to avoid the very long waiting times than those patients undergoing endoscopy alone**.

There were **several drivers that lengthened diagnostic pathway average timeframes,** some related to the nature of the pilot and evaluation itself, and which could be potentially manageable in a non-pilot context. For instance, patients who were on the waiting list longest were prioritised for Cytosponge, the time between referral and triage may have been artificially elongated compared to what it would be in a future roll-out. Likewise, as this was the first time that the Cytosponge test was implemented at the sites, this may have increased the time taken to triage patients, administer the test, and provide test results compared to what it would be if Cytosponge was being used as a routine tool. This is also supported by evidence that the **waiting time until the end of the diagnostic pathway also decreased the longer Cytosponge was in place.** The number of patients with long diagnostic waiting times decreased during the pilot amongst both Cytosponge and counterfactual patients.

Cytosponge is a patient-friendly and acceptable procedure to patients in secondary care settings. Approximately 93% of patients accepted the offer to complete a Cytosponge test. This aligns with the high levels of satisfaction observed in the Patient Experience survey. Evidence also indicates that Cytosponge is a safe procedure to triage patients with reflux symptoms. 94.8% of patients who attended the test appointment successfully completed the Cytosponge test, with the majority of patients (86.9%) needing only one attempt to swallow the sponge. **No serious adverse events were reported by sites during the evaluation period**.

Patient experiences of Cytosponge

Most patients (82%) were satisfied with their experience of the Cytosponge test. Perceptions of respect and dignity during the testing process were overwhelmingly positive. Reasons for high levels of satisfaction included Cytosponge being a less invasive procedure compared to an endoscopy, having more confidence in the method of sampling cells rather than assessing visually, fewer staff and facilities being needed, and the timeliness and speed of getting an appointment and receiving an answer and peace of mind.

There were **variations in patient satisfaction by test result.** Patients were more likely to be happy with their Cytosponge test compared to waiting for an endoscopy if their original issue was resolved. Patients were less likely to be happy if their original issue was not resolved. Other reasons for dissatisfaction included problems with swallowing the Cytosponge, its retrieval, and not understanding the details of what the test results show.

Clear explanations by professionals enabled patients to make informed decisions about the offer of the Cytosponge test. Almost all patients reported that they understood, at least to some extent, the explanations regarding Cytosponge, what would happen during the test and the purpose of the test. Information provided (e.g., a leaflet) was positively received and informed the choices of almost all patients.

Most patients experienced no pain or just mild pain during or immediately after the test. More patients (66%) reported experiencing some level of discomfort rather than pain during or after the test, with around 22% experiencing severe discomfort. Discomfort usually occurred when patients were swallowing the device and/or when it was removed. Despite this, most patients (87%) were able to swallow the sponge on the first attempt. **Most patients were unconcerned with the level of discomfort they experienced during the test**. Patient expectations also played a role in the level of discomfort experienced, as well as their overall experience.

Most patients surveyed indicated that they were satisfied regarding the time they waited to receive their Cytosponge test results. Around a fifth of patients (19%) surveyed reported that they received their test results in under two weeks, with the majority (59%) reporting receiving their test results in two to four weeks. In patient interviews, those with longer wait times often still stated they were happy as they understood why the process was longer than previous endoscopy experience, in which results were often received the same day. Patients interviewed who received an onwards referral for endoscopy were positive about the timeframes this involved.

Most patients interviewed were pleased with their contact method, but this was often contingent on the nature of the results. Most patients surveyed reported that they received their test results by mail (67%) or by phone (28%). Patients interviewed indicated that, had their results been positive, they would have preferred a personal phone call with the ability to ask questions over receiving a letter.

There were **some differences by sex in the experiences of Cytosponge patients**. The most noticeable differences included higher levels of reported satisfaction with the test amongst men, male patients more likely to report being happy with being offered Cytosponge instead of waiting for an endoscopy, lower levels of reported pain by men, women more likely to report discomfort after their test and a higher proportion of women reporting they were given information about being taken off the waiting list for endoscopy. Overall, these **results suggest that men had a more favourable experience of the Cytosponge test compared to women**.

Most patients surveyed reported having a clear understanding of the next steps in their pathway, but there were differences by result type and degree to which patients felt their problems were solved. Patients' understanding of what their next steps were differed by the type of result they received. Most patients received a negative test result and were subsequently discharged. Few patients with negative results did not feel their next steps were clear. Patients who felt their original issue was resolved at least to some extent were also more likely to report that they understood what their next steps were (89%) compared to those who did not feel their original issue was resolved (61%).

Impact of Cytosponge on patient inequalities

There is a lack of clear evidence regarding inequalities in accessing a diagnosis based on levels of deprivation. Amongst patients who successfully completed a Cytosponge test, the distribution of test results was similar across IMD quintiles. Whilst the proportion of patients discharged or monitored was higher for the 1st IMD quintile (i.e., most deprived 20% of the population with 63.6%) compared with other groups such as the 5th IMD quintile (i.e., least deprived 20% of the population with 46.3%), which could suggest a health inequality, those in the 5th IMD quintile were also more likely to have an unknown or “Other” subsequent action recorded. Given the unclear discharge status of these groups, no clear conclusions can be drawn regarding inequalities in accessing a diagnosis related to deprivation.

There were no clear differences by deprivation levels in the median time to the end of the diagnostic pathway amongst either Cytosponge or counterfactual patients. The median time from triage to the end of the pathway was approximately 48 days for Cytosponge patients across all IMD quintiles, suggesting no health inequalities based on the data available.

There were similar proportions of test results and subsequent actions amongst men and women. However, the risk of BO and other reflux-related disorders is higher amongst men than women (Fass et al., 2021). The **similar proportions of test results and subsequent actions observed across sexes could therefore indicate a potential health inequality in access to a diagnosis for men**. However, this needs further examination as there may also be an impact of selection bias affecting the representatives of the Cytosponge group.

Overall, the **proportion of patients with a positive Cytosponge test result increased with older age, alongside a corresponding increase in endoscopy referrals**. This indicates that older patients were at a higher risk of BO and were appropriately prioritised through the diagnostic pathway. This is expected as the severity and incidence of BO and other gastroesophageal reflux disease complications increase with age (Chait, 2010), therefore suggesting that **these differences across age groups are not likely to relate to age-related inequalities in access to diagnosis or outcomes**.

Due to small sample sizes in some ethnic groups, **no robust conclusions could be drawn with confidence regarding ethnic inequalities in Cytosponge test results and subsequent actions**. Similarly, amongst patients who completed the patient experience survey, comparisons by ethnicity were unlikely to be meaningful due to the lack of representation from non-white ethnic groups.

Overall, future service provision should continually be informed by patient inequalities to improve patient outcomes and access to care. It also remains important to continue monitoring whether future service provision is meeting the needs and delivering strong outcomes for all patients. Further monitoring and evaluation and additional quantification of the role of health inequalities (e.g., by deprivation level or ethnicity) in the Cytosponge programme using larger samples of patients over longer timeframes is needed to draw more robust conclusions.

Enablers and barriers to the use of Cytosponge

Key factors that either facilitated (‘enablers’) or hindered (‘barriers’) this Cytosponge pilot programme use case – i.e., as a triage tool in secondary care for patients with low-risk reflux symptoms on a routine referral – were identified through discussions with a range of NHS staff involved at both a national level and local level (in all Cytosponge delivery sites).

A dedicated Cytosponge team was deemed imperative to successfully implement a scalable and sustainable service. This was reflected in both site- and national-level perspectives. The volume of administrative support required was explained to be unrealistic for clinical personnel to manage alongside their clinical duties. Dedicated administrative support during service set-up and throughout service delivery allowed better management of contracting and delivery of services. Alongside administrative roles, the clinical roles needed to be filled by experienced nursing staff and consultants. The most experienced nurses with knowledge regarding endoscopy services, exhibited the most confidence delivering the Cytosponge procedure. This supported the delivery of high-quality patient care. In addition to staffing, a dedicated but flexible physical space for Cytosponge procedures made it easier for sites to deliver services.

Barriers to effective implementation of Cytosponge included a lack of awareness of specific guidance and/or support available for administrative and contracting elements of the process. Linked to this, a lack of targeted support (e.g., support specifically related to individual trust contracting processes) meant additional effort was required by sites. This sometimes-meant clinical staff needed to undertake more administrative work, which competed with their focus on clinical duties, especially during the COVID-19 pandemic. Inaccuracy of patient number predictions at service set-up was a challenge to the development of suitable resourcing.

Lack of knowledge, education, and guidance had an impact on clinician confidence in Cytosponge test results. This influenced the degree to which Cytosponge clinical guidelines were followed, for instance for onward referrals (e.g., patients being referred for an onward endoscopy following a negative Cytosponge test, instead of a Cytosponge repeat test).

Some challenges and barriers were related to the pilot nature of the programme and would not necessarily be present, or would be different, in a rolled out Cytosponge service. For a possible future national roll-out of Cytosponge, the role of NHS England, Cancer Alliances, ICBs and trusts should be clearly defined.

There was **some variability in how the Cytosponge programme was implemented across different sites**. Variations were seen in areas such as referrals (e.g., GP or endoscopy waiting list), triage (e.g., consultant or nurse led), review of pathology reports (e.g., consultant or nurse led), communication of results to patients (e.g., letter or phone call), and the process for managing patients who did not attend tests. Variability can be seen as a positive in some instances due to the flexibility required when trying to implement change in heterogeneous settings (e.g., an experienced clinical nurse specialist could carry out the triage review in some sites, but in others, it would need to be the consultant). However, variability could also be viewed as a challenge in the same situation. For instance, a consultant may be needed for the triage review, but may not be appropriately engaged in the service and therefore delaying the amount of time required to triage patients.

Cost effectiveness of Cytosponge and budget implications

Including Cytosponge in the diagnostic pathway is highly cost effective relative to an endoscopy-only programme, based on a moderate cost saving relative to a minimal reduction in quality adjusted life years (QALYs).

In the cost effectiveness model (CEM) base case, the Cytosponge programme results in a per-patient cost-saving of £421.57and a very slight decrease in QALYs of 0.0041.

The difference in QALYs between the Cytosponge and endoscopy-only programme is minimal. The small difference in QALYs is driven by modelling assumptions of a shorter time from referral to diagnosis (46 days) and higher (perfect) sensitivity in the endoscopy-only programme. However, a difference of 0.0041 QALYs between programmes is equivalent to a difference of 1.5 days, highlighting the extremely small nature of this decrease over a lifetime.

The five-year net budget impact of introducing Cytosponge nationally is a budget saving of between ~£10 million and ~£33 million. A budget saving is realised in the first year, and then in every subsequent year. The annual saving also increases year on year. The actual cumulative saving over five years depends on the initial share of eligible patients assigned to Cytosponge testing, the increase in patients each subsequent year and the total number of potentially eligible patients overall:

- If the initial share of eligible patients assigned to Cytosponge in year 1 is 10%, with an increase of 10 percentage points every year, the net budget saving over 5 years is £10,297,798.

- If the initial share of eligible patients assigned to Cytosponge in year 1 is 50%, with an increase of 10 percentage points every year, the net budget saving over 5 years of £23,748,419.

- If the initial share of eligible patients assigned to Cytosponge in year 1 is 90%, with an increase of 10 percentage points every year, the net budget saving over 5 years of £32,993,996.

Given the very small difference in QALYs accrued, **the main driver of per-patient cost savings in the Cytosponge programme is the large proportion of avoided endoscopies** during the diagnostic pathway in the Cytosponge programme.

The price of the Cytosponge test is a key driver of these results. There is a linear relationship between the price of the Cytosponge test and cost-effectiveness: for every 1% decrease in the price of Cytosponge, the NMB increases by 1%. Similarly, for every 1% decrease in the price of Cytosponge the net budget savings increase by 0.8%. This shows that a change in the price of the Cytosponge test has a significant effect on both the cost-effectiveness of the Cytosponge programme and budget savings to the NHS in a world with Cytosponge. However, the cost effectiveness and budget savings are maintained even if higher price points are assumed for the Cytosponge test.

The Cytosponge programme is therefore both a cost-effective and budget saving intervention relative to the standard of care when used as a triage tool in secondary care.

Resources required for a national roll-out of Cytosponge

Effective service delivery must be supported by a dedicated and experienced Cytosponge clinical team as well as dedicated administrative support staff, all with protected time in the service. These are amongst the most impactful enablers of effective Cytosponge service delivery.

Roll-out should also be supported by resources to improve clinician confidence in the Cytosponge test results. This could be achieved through an education programme being developed and rolled-out in primary, secondary and community care.

To determine service scalability, a scalability model has been developed to support decision-making around the allocation of resources for a national level roll-out. Based on inputted data on a range of relevant criteria into the model, this interactive Excel document will display the range of FTE staff (i.e., nurses, consultants, etc.) and treatment rooms required to run the service effectively and enable any NHS trust to better understand the resources required in terms of nurse hours, consultant hours, room time and time for administrative tasks to scale or establish a Cytosponge service based on their trust requirements.

The budget impact models (BIM) show that the initial value of the resources required for a national roll-out is between ~£1 million and ~£12 million. This provides an estimate of the financial requirements in the first-year post-launch in terms of the resources accounted for in the BIM (acquisition costs of diagnostic tests, adverse event costs, outpatient appointments, etc.). It is based on the direct variable costs of medical care and does not explicitly account for costs such as overheads, or initial outlay costs (e.g., education initiatives prior to commencement).

The BIM is based on an incident eligible population of 15,121 in year 1. Assuming the initial share of the population assigned to Cytosponge in year 1 is 10%, the spend during the diagnostic pathway for those assigned to the Cytosponge programme is £1,321,426. Assuming an initial share of 90%, the spend is £11,892,838.

Given the budget impact results, it is likely that the cost of investment can be 'covered' by some of the budget that would otherwise be dedicated to endoscopy provision for the same number(s) of patients in a 'world without Cytosponge'.

Based on the evaluation findings, a number of **specific and actionable recommendations for a national roll-out of Cytosponge** are made in relation to communication, decision making, training and implementation. These include clarifying, establishing and communicating a) administrative and clinical roles required, and b) support services; supporting the use of the scalability model to inform decision making; developing and implementing a training programme for clinicians; and examining strategies to reduce time taken to receive Cytosponge test results. In addition, other recommendations relevant to specific aspects of the Cytosponge programme and any future roll-out are made in the relevant sections throughout the report.

Key evaluation messages

Q1. What impact does Cytosponge (delivered in secondary care as a routine referral triaging tool) have on endoscopy demand?

1. Cytosponge testing effectively reduced endoscopy demand in secondary care by 78% in patients who completed a Cytosponge test.
2. There is some evidence that Cytosponge helped to triage patients (both high and low risk), as most BO cases were found on the endoscopy outcomes of patients with positive test results, while no BO cases were detected in patients who had a negative test result but nonetheless underwent an endoscopy.
3. The effectiveness of Cytosponge in reducing endoscopy demand increased over time during the pilot period.

Q2. What impact does Cytosponge have on patient outcomes?

1. Cytosponge patients were appropriately prioritised through the pathway based on their test result and urgency for endoscopy.

2. Cytosponge can triage patients accurately and is unlikely to miss BO diagnoses compared to endoscopy alone.
3. Cytosponge patients were tested quickly following triage and waited on average three weeks to receive their test result.
4. Cytosponge lengthened timeframes to the end of the diagnostic pathway overall, in particular for patients receiving a non-urgent endoscopy referral following their Cytosponge test.
5. Patients who received a Cytosponge test waited similar times to receive a BO diagnosis compared to counterfactual patients.
6. Cytosponge is an acceptable and safe procedure in secondary care settings, and no serious adverse events were reported during the evaluation period.

Q3. What impact does Cytosponge have on the diagnostic experience of patients?

1. 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.
2. Clear explanations by professionals enabled patients to make informed decisions.
3. 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.
4. Most patients were unconcerned with the level of discomfort they experienced during the test.

Q4. How does Cytosponge affect patient inequalities, both in access to a diagnosis, and outcomes?

1. Similar proportions of test results and subsequent actions across sexes could indicate a potential health inequality in access to a diagnosis for men, but requires further examination.
2. Differences across age groups are not likely to indicate age-related inequalities in access to diagnosis or outcomes.

Q5. What are the key enablers and barriers to the implementation of Cytosponge in secondary care?

1. A dedicated Cytosponge team of administrative support roles and clinical roles was crucial for a successfully implemented, scalable and sustainable service, together with a dedicated but flexible physical space.
2. Lack of knowledge, education and guidance had an impact on clinician confidence in Cytosponge test results.
3. Some challenges and barriers were related to the pilot nature of the programme and would not necessarily be present, or would be different, in a rolled out Cytosponge service.

Q6. What are the cost-effectiveness and budget impact of Cytosponge when used as a diagnostic triage tool in secondary care?

1. Cytosponge programme resulted in a per-patient cost-saving of £421.57 and a very slight decrease in QALYs of 0.0041.

2. The five-year net budget impact of introducing Cytosponge nationally depends on the proportion of patients assigned to Cytosponge instead of endoscopy-only in the first year, e.g.
    a. An initial 10% share of eligible patients assigned to Cytosponge in year 1, with an increase of 10 percentage points every year, gives a net budget saving over 5 years of £10,297,798.
    b. An initial 90% share of eligible patients assigned to Cytosponge in year 1, with an increase of 10 percentage points every year, gives a net budget saving over 5 years of £32,993,996.
3. A change in the price of the Cytosponge test has a significant effect on both cost-effectiveness and budget impact.
    a. For every 1% decrease in the price of Cytosponge, the NMB increases by 1%
    b. For every 1% decrease in the price of Cytosponge the net budget savings increase by 0.8%.
4. Cytosponge programme is both a cost-effective and budget saving intervention.

Q7. What investment would be required for a national roll-out of this programme?

1. Budget impact models show that the initial value of the resources required for a national roll-out is between ~£1 million and ~£12 million.
2. It is likely that the cost of investment can be ‘covered’ by some of the budget that would otherwise be dedicated to endoscopy provision.

SECTION 1: INTRODUCTION

This report provides the final summative results and findings of the evaluation of using Cytosponge for triaging routine referrals in NHS England (NHSE). The purpose of this document is to:

- Provide an overview of the evaluation programme and details of the methodologies applied by each of the evaluation workstreams.
- Bring together evidence from the multiple workstreams to address each of the evaluation questions.
- Reflect on the available evidence and provide overarching conclusions to support decisions to be taken by NHSE and the potential roll-out of the programme more widely.

The Cytosponge pilot programme

Gastro-oesophageal reflux disease (GORD) is a relatively common condition with approximately 10 – 20% of the population experiencing some degree of symptoms, including heartburn, acid reflux and regurgitation (El-Serag et al., 2014). A variety of demographic and lifestyle factors may increase the risk of gastro-oesophageal reflux, including older age, male sex, intake of analgesics, consumption of certain types of food and drinks, smoking, high body mass index, and limited physical activity (Yamasaki et al., 2018). Some patients with these symptoms may already have or develop Barrett's oesophagus (BO), a precursor to oesophageal cancer (OC). BO is currently diagnosed via endoscopy following a GP referral to a gastroenterologist or other specialist in secondary care.

The NHS Long Term Plan aims to improve cancer outcomes through early diagnosis and treatment. Endoscopy services across England were severely affected by COVID-19, which resulted in longer waiting times for patients. For instance, a 30% reduction in diagnostic endoscopies was reported for the period between January and April 2020, compared with the same period in 2019, with an estimated 750 oesophagogastric cancers going undiagnosed (Markar et al., 2020). This created backlogs and delays which contributed to ongoing pressure on endoscopy services.

Cytosponge is a diagnostic tool that can help triage patients at higher risk of BO. Cytosponge, when used as a triaging tool in secondary care as part of the endoscopy pathway, presents a potential means of accelerating the recovery of elective care services post COVID-19 and may support the cancer ambitions in the NHS Long Term Plan. This led to the decision to pilot the Cytosponge tool in secondary care.

In January 2021, NHSE launched a pilot of the Cytosponge tool for triaging patients with low-risk reflux symptoms on a routine referral diagnostic pathway in the secondary care setting. The pilot was launched across 17 Cancer Alliances and c. 30 hospital sites across England. The intended outcomes of the pilot were:

- Reduced overall healthcare resource use and associated costs by replacing some endoscopies with a Cytosponge test.
- Reduced overall waiting times/waiting lists (demand) for endoscopy.
- Improved clinical outcomes.

- Improved patient experiences.
- Reduced health-related inequalities.

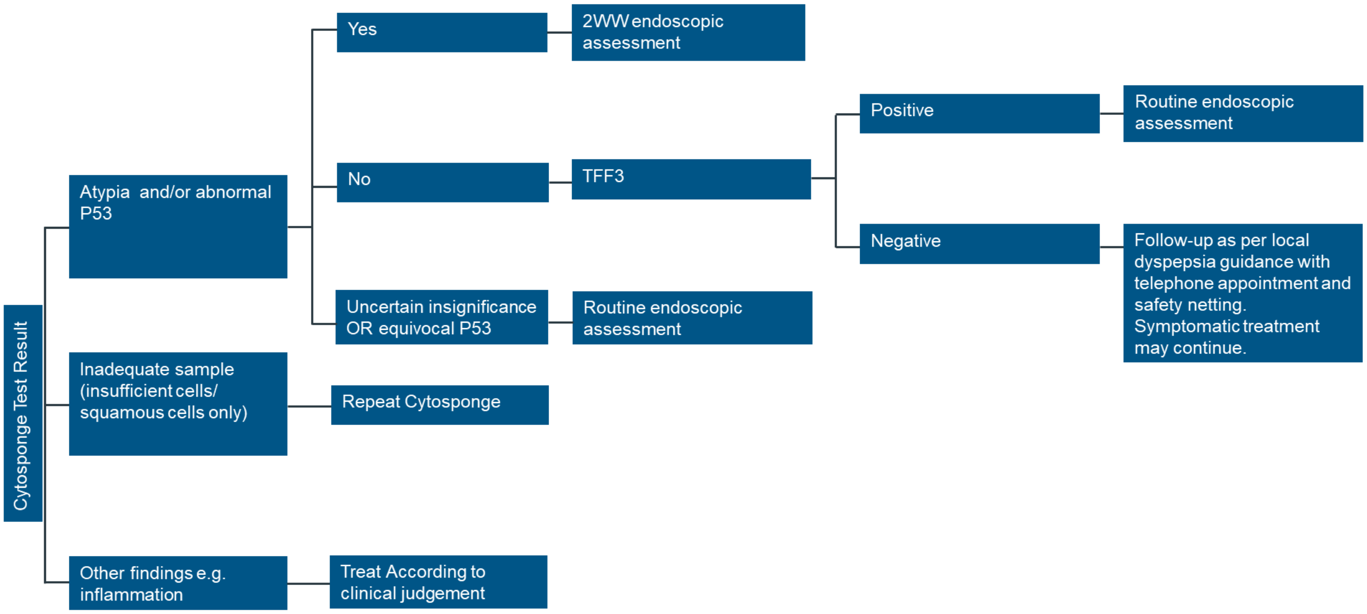
Patient diagnostic pathway clinical guidance

An expected benefit of Cytosponge as a triage tool in the secondary care setting for patients with low-risk reflux symptoms is that it reduces the number of onward referrals for an endoscopy.

For the pilot, eligible patients waiting for a routine endoscopy on the standard diagnostic pathway were offered a Cytosponge test as an alternative to their endoscopy. The patients that accepted the offer were subsequently removed from the endoscopy pathway and placed on an alternative Cytosponge pathway.

Once patients completed their Cytosponge test, their onwards diagnostic pathway was determined by a combination of the Cytosponge pathology results and clinical judgement. The key pathology results of interest included the presence of Atypia (abnormalities in the cell tissue) and the presence of TFF3 (a strong candidate biomarker in the diagnosis of Barratt's oesophagus). Figure 2 depicts the possible diagnostic pathways for patients who received Cytosponge, depending on the result of the test.

Figure 2. Follow up required for Cytosponge sample results including endoscopy guidance where required



The pathway indicates that patients with a negative Cytosponge result, indicated by results of 'Atypia and/or abnormal P53' – No, and 'TFF3' – Negative, should be removed from the endoscopy referral pathway and followed-up as per the local dyspepsia guidance for symptomatic treatment. This reduces the number of people who were originally placed on the endoscopy waitlists due to their reflux symptoms but had no pathological indicators of BO. With the waitlist reduced, there is also an expectation of shorter wait times for patients who present with indicators of BO and require endoscopy for their diagnosis.

There are four possible circumstances under which patients remain on the endoscopy wait list following their Cytosponge test:

- Patients with a positive Cytosponge result: Atypia and/or abnormal P53 – Yes. These patients should always receive an urgent confirmatory endoscopy.
- Patients with a positive Cytosponge result: Atypia and/or abnormal P53 – No; TFF3 – Positive. These patients should be referred for an onwards endoscopy on the routine assessment diagnostic pathway.
- Patients with inconclusive Cytosponge results: These patients may either be offered a repeat Cytosponge procedure or treated according to clinical judgement. In some cases, patients may present with negative Cytosponge tests but the presence of histopathological indicators of BO such as Ulcer Slough or Intestinal Metaplasia. In these cases, a clinician may refer a patient for an onwards endoscopy to confirm a diagnosis despite receiving a negative Cytosponge test. Similarly, patients who complete multiple repeat Cytosponge tests with consistently inconclusive results may also be referred for an endoscopy as they may not be able to complete the test.
- The Cytosponge test may identify other benign findings that are not indicators of BO such as inflammation or candida. These patients should also be treated according to clinical judgement at the time of testing, which may include being referred for an endoscopy.

The Cytosponge pilot programme evaluation

Following the initiation of the Cytosponge pilot in January 2021, an evaluation was undertaken by IQVIA on behalf of NHSE. The evaluation, from design and strategy development to final reporting, ran from August 2021 until August 2023. Various data collection activities and analyses were undertaken under four workstreams (see below and Section 2). These used data collected from patients between February 2021 and March 2022. The evaluation addressed three core evaluation objectives:

1. To determine the extent to which the intended outcomes of the programme were achieved along with identifying unintended consequences.
2. Support a decision on a potential national roll-out.
3. Inform future NICE appraisal processes (e.g., the NICE Diagnostic Assessment Programme, DAP).

The evaluation aimed to address evidence gaps specific to this use case for triaging routine referrals within the secondary care setting. The majority of previous clinical studies were conducted in the primary care setting and no economic analyses have been completed for this use case. This evaluation adds to the evidence base and addresses gaps in the following ways:

- **Safety, effectiveness, and acceptability:** a case-control study was performed across UK hospitals to evaluate the safety, acceptability, and accuracy of the Cytosponge test for the diagnosis of BO compared with endoscopy. This evaluation provides further evidence on the impact of Cytosponge on both outcomes and patient experience, however, the safety and diagnostic accuracy of Cytosponge were deemed out of scope due to previous research.
- **Reduced endoscopy demand:** this has not been the explicit focus of previous studies. This evaluation determines, within the time horizons of the pilot, the impact of introducing Cytosponge on overall demand for upper gastrointestinal (GI) endoscopy and whether Cytosponge is likely to help reduce waiting times for patients.

- **Efficient use of NHS resources:** This evaluation provides an economic analysis to determine the overall impact of Cytosponge when used as a triage tool on NHS budgets (higher or lower overall cost of the pathway) and, if it represents an increased cost, whether it is cost-effective.
- **Scaling:** previous studies have not focused on the potential to scale Cytosponge nationally in NHSE. The evaluation addresses this question and provides findings to support decisions regarding a national roll-out.

It should be noted that this evaluation was not intended to explore diagnostic accuracy. Patients did not receive concurrent Cytosponge and endoscopy tests as part of the pilot, therefore, the true sensitivity and specificity could not be evaluated.

Evaluation questions, framework and design

Evaluation questions

In order to address the evaluation objectives, the evaluation was framed around seven key evaluation questions:

1. What impact does Cytosponge (delivered in secondary care as a routine referral triaging tool) have on endoscopy demand?
2. What impact does Cytosponge have on patient outcomes?
3. What impact does Cytosponge have on the diagnostic experience of patients?
4. How does Cytosponge affect patient inequalities, both in access to a diagnosis and outcomes?
5. What are the enablers and barriers to the implementation of Cytosponge in secondary care?
6. What is the cost-effectiveness and budget impact of Cytosponge, when used as a diagnostic triage tool in secondary care?
7. What resources would be required for a national roll-out of this programme?

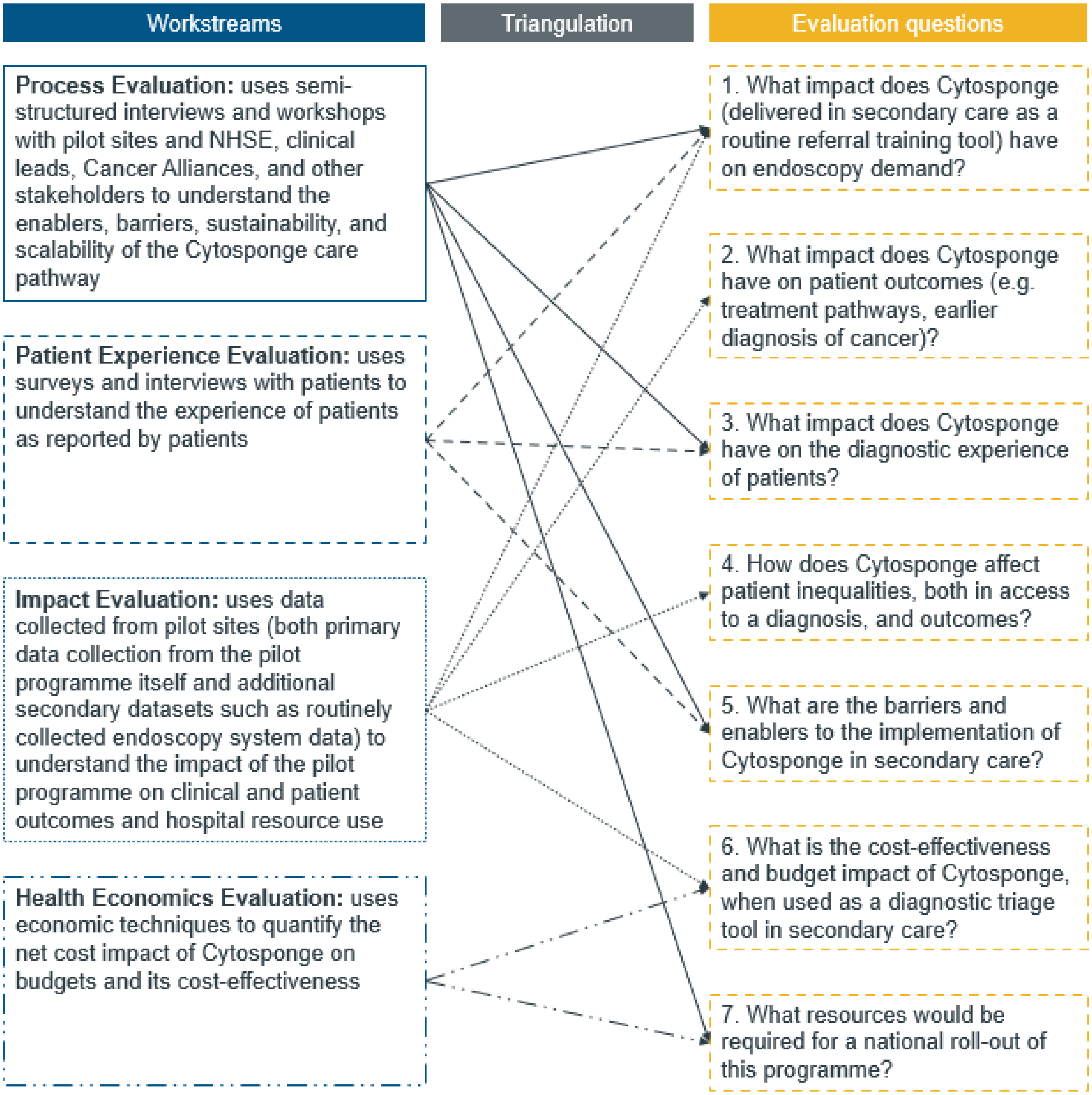
Evaluation framework and design

The evaluation was designed to answer the evaluation questions using a range of methodologies delivered through four workstreams:

- **Process Evaluation –** uses semi-structured interviews and workshops with pilot sites and NHSE, clinical leads, Cancer Alliances, and other stakeholders to understand the enablers, barriers, sustainability, and scalability of the Cytosponge pathway.
- **Patient Experience Evaluation –** uses surveys and interviews with patients to understand the experience of patients as reported by patients.
- **Impact Evaluation –** uses data collected from pilot sites (both primary data collection from the pilot programme itself and additional secondary datasets such as routinely collected endoscopy system data) to understand the impact of the pilot programme on clinical and patient outcomes and hospital resource use.
- **Health Economics Evaluation –** uses economic techniques to quantify the net cost impact of Cytosponge on budgets and its cost-effectiveness.

Each evaluation question was explored using data and analysis by one or more workstreams. For evaluation questions assessed using data from more than one workstream, workstream findings were compared, triangulated and aligned against each other to arrive at a holistic analysis. Figure 3 displays which workstreams provided data relevant to each of the evaluation questions.

Figure 3. Workstream mapping to evaluation questions



Process Evaluation: uses semi-structured interviews and workshops with pilot sites and NHSE, clinical leads, Cancer Alliances, and other stakeholders to understand the enablers, barriers, sustainability, and scalability of the Cytosponge care pathway

Patient Experience Evaluation: uses surveys and interviews with patients to understand the experience of patients as reported by patients

Impact Evaluation: uses data collected from pilot sites (both primary data collection from the pilot programme itself and additional secondary datasets such as routinely collected endoscopy system data) to understand the impact of the pilot programme on clinical and patient outcomes and hospital resource use

Health Economics Evaluation: uses economic techniques to quantify the net cost impact of Cytosponge on budgets and its cost-effectiveness

1. What impact does Cytosponge (delivered in secondary care as a routine referral training tool) have on endoscopy demand?
2. What impact does Cytosponge have on patient outcomes (e.g. treatment pathways, earlier diagnosis of cancer)?
3. What impact does Cytosponge have on the diagnostic experience of patients?
4. How does Cytosponge affect patient inequalities, both in access to a diagnosis, and outcomes?
5. What are the barriers and enablers to the implementation of Cytosponge in secondary care?
6. What is the cost-effectiveness and budget impact of Cytosponge, when used as a diagnostic triage tool in secondary care?
7. What resources would be required for a national roll-out of this programme?

Each workstream was staffed with specialists with the appropriate competencies. Regular and ongoing communication and dialogue between the workstream teams ensured that data and analysis from each individual workstream informed the evaluation questions in a holistic manner. It also enabled data and findings to be compared, triangulated against and feed into information from other workstreams to ensure robust overall analysis. For example, insights from the Patient Experience workstream allowed for the Process Evaluation workstream to consider insights from patients regarding how Cytosponge had been delivered.

Sites were asked to review and provide data for patients offered a Cytosponge between February 2021 to March 2022 and include follow up endoscopy data up to the end of June 2022. The timeframe allowed for around 16 months of follow-up for patients seen at the very start of the pilot and 3 months of follow-up data for patients seen up to the end of March 2022. However, this only allows for short-term outcomes to be measured directly. This limitation has been acknowledged by NHSE and there is potential for a separate follow-up evaluation to take place to assess longer term outcomes (e.g., two years post Cytosponge being administered to a patient).

The number of Cytosponge procedures administered between February 2021 and March 2022, and other summary data, is provided in this report’s appendices.

A more detailed overview of the pilot programme and its evaluation can be found in other supplementary working documents (e.g., statistical analysis plan, model analysis plan) which are separate to this report.

Evaluation report structure

The remainder of this report is structured as follows:

- Section 2 provides summaries of the evaluation implementation for each workstream, including the purpose and methodological approach for each workstream. It also provides summaries of the data sources for each workstream and potential limitations or challenges.
- Section 3 presents the key findings for each evaluation question using data and analysis from the relevant workstreams.
- Section 4 draws together the main conclusions from the evaluation to consider and inform a wider roll-out of Cytosponge.

SECTION 2: EVALUATION PROCESS

This section provides an overview of the purpose and methodological approach for each workstream within the Cytosponge evaluation. It focuses on the actual implementation of the workstreams, rather than detailed design, which can be found in other supplementary working documents (e.g., Impact Evaluation statistical analysis plan, Health Economics Evaluation budget impact model (BIM) and cost effectiveness model (CEM) plans).

Additional high-level analysis was completed on data provided by the sites via the Monthly Management Information returns (aggregate dataset) and the Cytosponge pathology results data provided by Cyted. These findings supplement the information elicited from the evaluation workstreams. Tables depicting the results can be found in Appendix A and Appendix B.

Process Evaluation

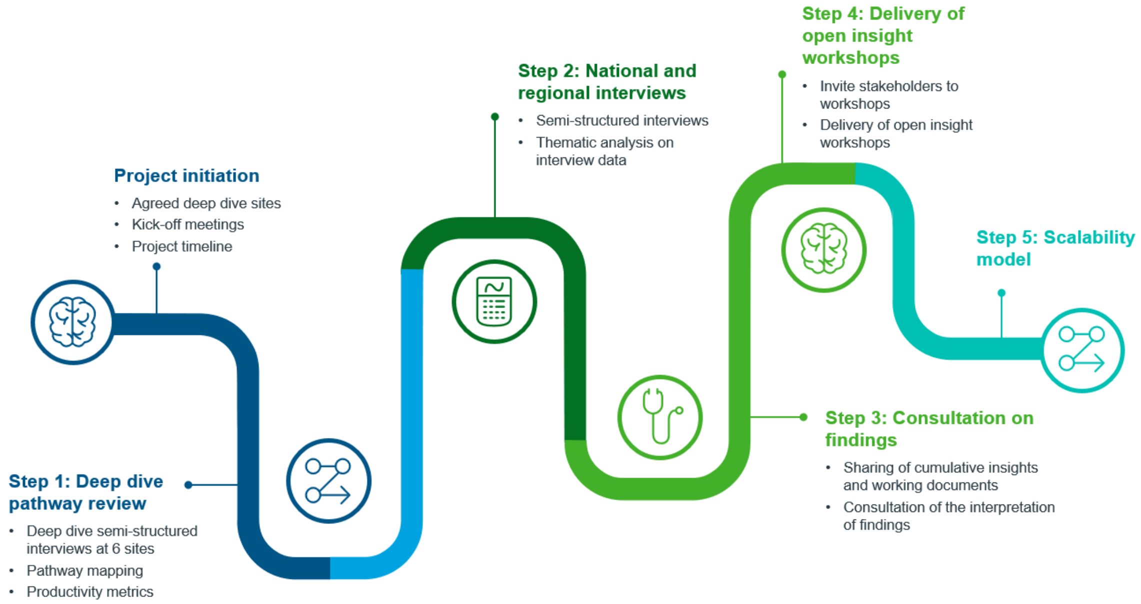
Purpose

The purpose of the process evaluation was to generate an understanding of the key enablers (i.e., factors that facilitated or helped) and barriers to implementing the Cytosponge pathway, as well as its future sustainability and scalability.

Methodology

A combination of qualitative and quantitative research methodologies (Figure 4) were used to determine whether the Cytosponge programme had been implemented as intended and the extent to which the anticipated outputs had been achieved. Data was collected through semi-structured interviews, pathway mapping, and collaborative workshops with pilot site staff (a ‘deep dive’ in designated sites).

Figure 4: Steps and methodologies in the Process Evaluation



Step 1: Six site-level ‘deep dives’

The first step in the process evaluation was undertaking in-depth interviews with 22 individuals across six pilot sites. These were selected in collaboration with NHSE to provide a broad range of experiences and views – e.g., a mix of rural and urban geographies, and sites at different stages of rolling out Cytosponge (see Table 1). The interviewees included consultant gastroenterologists, Cytosponge nurses, endoscopy nurses, service managers, endoscopy secretaries, and Cytosponge coordinators.

Table 1. Summary of sites selected for the 'deep dives'

Site	Region	Alliance	Procedures (up to October 2021*)	Inclusion rationale
1. Salford Royal NHS Foundation Trust	Northwest	Greater Manchester	91	- First site to go live - Strong clinical engagement and leadership
2. East and North Hertfordshire NHS Trust (Lister Hospital)	Midlands	East of England	168	- High volume Cytosponge service and well embedded in routine practice
3. University Hospitals Plymouth NHS Trust	Southwest	Peninsula	30	- Geographic location of mix of urban and rural communities - Consultant led follow-up (rather than nurse)
4. East Kent Hospitals University Foundation Trust (William Harvey Hospital)	Southeast	Kent and Medway	71	- Fully nurse led clinics - Full time admin co-ordinator
5. Barking Havering Redbridge University Trust (BHRUT – Queens Hospital)	London	Northeast London	33	- Innovative investment into identifying and increasing triaging opportunities (training, advertising services to GP)
6. North Cumbria Integrated Care NHS Foundation Trust (Cumberland Infirmary)	Northeast and Yorkshire	Northeast and Cumbria	30	- High onward endoscopy rates - A community services hospital

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*Site selection for the deep dives took place in October 2021. The number of procedures up to October 2021 were considered to ensure a range of sites were included based on their delivery status at the time of site selection.

Step 2: National and regional level stakeholder interviews

National and regional level stakeholders were interviewed (six interviews in total, with more than one attendee at some of the interviews) and data from these interviews was combined with data from the site interviews to produce a thematic analysis of findings. National and regional level stakeholders included representatives from the Cancer Alliances, Cyted, Medtronic, Cambridge University, a site that had dropped out of the pilot project, the Cytosponge Oversight Group, and the NHSE Cancer Programme. Although most interviewees covered similar themes, they sometimes had different perspectives on the same issues. Relational analysis was therefore undertaken to help compare and describe the range of views.

Step 3: Clinical consultation

Following the interviews with site, regional and national stakeholders, the evaluation team presented preliminary findings to a clinician within the NHSE Cytosponge Oversight Group. The meeting was conducted to elicit final clinical or operational insights before presenting summary findings back to the sites via open-insight workshops. The clinician provided verbal feedback during the meeting which was incorporated into the presentation for the workshops.

Step 4: Open-insight workshops

Four open-insight workshops were organised to deliver the findings from the deep dives and national interviews to all of the participating pilot sites. The focus was on detailing the enablers, barriers, and recommendations for a national level roll-out. The evaluation team communicated the findings, with a particular focus on key issues, ahead of the workshops. The workshops provided the opportunity for the evaluation team to probe for deeper insights in specific areas.

Sites were grouped by integrated care system (ICS) and location where applicable, and workshops were scheduled to accommodate the availability of site personnel. The site teams were encouraged to provide any further comments on the enablers and barriers identified or raise any areas of concern that had not already been addressed.

Step 5: Scalability model

A scalability model was developed to support resource allocation decision-making for a national level roll-out. It uses inputs from qualitative data collected during site-level interviews and quantitative data from the sites' monthly management data. The scalability model is an interactive Excel workbook that provides the following outputs:

- Trust-expected endoscopy demands.
- Proportion of patients that may not accept the Cytosponge.
- Number of potential incomplete Cytosponge procedures.
- Estimated time spent per Cytosponge procedure.
- Estimated time spent on patient-related administrative tasks (e.g., collecting patient information) outside of the treatment room.

Method of analysis

No patient level data was gathered by this workstream. Data obtained from pathway mapping activities was captured using MS Office applications (e.g., Visio) on secure, encrypted IQVIA laptops. Thematic analysis was carried out using qualitative analysis software programmes such as Atlas.ti.

Following the completion of interviews, the evaluation team considered all the insights developed and undertook thematic analysis, a systematic technique widely recognised for its rigorous approach to qualitative analysis. Six thematic analysis phases were followed, in line with best practice (Braun & Clarke, 2006).

1) *Data familiarisation* – initial reading of the interview notes.
2) *Generating initial codes* – initial comments and codes will be identified.
3) *Searching for themes* – initial codes are grouped to highlight commonalities between them.
4) *Reviewing themes* – codes and themes are cross referenced with other team members.
5) *Defining and naming themes* – theme names are refined and finalised.
6) *Production of the final report.*

Patient Experience Evaluation

Purpose

The purpose of the Patient Experience Evaluation was to determine the impact of the Cytosponge test on the diagnostic experience of patients. The evaluation findings were also used to support the Process and Health Economics Evaluations in relation to the Cytosponge test's effect on endoscopy demand and barriers and enablers to the implementation of the test.

Methodology

Quantitative and qualitative research methodologies were used to gather insight from patients about their experience of the Cytosponge test. Two measurements were designed to evaluate the impact of Cytosponge on the diagnostic experience of patients and the impact of Cytosponge on health inequalities. A survey questionnaire and semi-structured interview guide were developed by the evaluation team to assess patient experience.

Survey

The Patient Experience survey instrument was co-produced by the evaluation team, NHSE, healthcare professionals at Cytosponge sites, Cytosponge patients, and with support from colleagues from ENDOPREM (Neilson et al., 2021). The ENDOPREM survey instrument was used in question development due to its similarity in capturing patient experience during a comparable procedure (upper GI endoscopy). ENDOPREM guidance also ensured that the final Cytosponge survey instrument captured experience across the entire patient journey, not simply during the procedure itself. The survey aimed to gather data to help understand patient experiences, views and insights around four key areas:

- The impact of the Cytosponge test on the diagnostic experience of patients.
- The experience of receiving results and confidence in the nature of the test compared to an endoscopy.

- Subsequent effects in terms of adverse events or unintended consequences.
- The impact of the Cytosponge test on patient outcomes.

Cognitive testing

Cognitive testing of the questionnaire was carried out with volunteer patients (n=18). Feedback was gathered from the volunteers on the scope, relevance and clarity of the questionnaire.

Survey data collection and analysis

The survey was available and open online from 01 September to 20 November 2022. All patients who had been offered a Cytosponge from February 2021 to March 2022 were invited to participate, including those who did not accept the offer of the Cytosponge test or who failed to attend their appointment. The survey was administered by IQVIA with options to respond online, by phone and in a language other than English.

At the end of the fieldwork period, data was checked and verified, any missing or duplicate responses were removed and a final dataset was produced for analysis. Following the extraction of the final survey data from IQVIA's secure survey database QMP (Questionnaire Management Platform), Microsoft Excel was used to aggregate and summarise results, producing the cross tabulations for each level of reporting required. Microsoft Excel was also used to create visualisations for the report. Where high volumes of reporting outputs were required, visual basic code was used to automate their production. A suppression level was applied to all results in order to maintain the anonymity of respondents and ensure that results were derived from a reliable base size. As such, only data from groups comprising five or more respondents were included in analyses. Some statistical significance testing was carried out on select comparison variables of interest (e.g., sex). Further details on this testing are available in a separate report shared with NHS England. Following, the completion of the analysis, the survey results were validated by ENDOPREM and recommendations related to future questionnaires were developed.

A total of 352 patients completed the Patient Experience survey at a response rate of 26% (n=1,251 total invitations sent), providing an adequately powered sample to estimate results with a 95% level of confidence and 5% margin of error.

Participants who completed the survey comprised of 62% female and 38% male respondents (n=352). This compares broadly to the sex distribution of patients who were offered a Cytosponge test and were eligible to receive it based on the Impact Evaluation data (57% and 42%, respectively, n=1,549).

98% of survey participants were from a white background. Due to the small sample sizes of other ethnic backgrounds, all non-white respondents (2%) were grouped for analyses.

The age of survey respondents ranged from 25-84 years of age. Respondents were most likely to be in the 55-64 age group (31%, n=100) and least likely to be in the 75-84 age group (7%, n=22). This is different from those who were offered for a Cytosponge test based on the Impact Evaluation data. Most notably, patients aged <45 comprised 36% of the patient cohort based on Impact Evaluation data, whereas only 22% of patients aged <45 completed the Patient Experience survey. Likewise, the median age of patients between the two datasets was broadly the same was descriptively lower in the Impact Evaluation dataset than in the Patient Experience survey (i.e., 52 years vs 59 years, respectively). in the Patient experience survey).

Response rates were highest for patients who attended their Cytosponge test appointments in the South, East, and Midlands. There appeared to be no correlation between response rates for the interviews and acceptance of the Cytosponge test. Across all sites that submitted Cytosponge data for analysis, acceptance was over 90% at all sites.

The survey was available online only which limited the sample to patients who provided a valid e-mail address and had internet access.

Semi-structured interviews

In-depth, semi-structured interviews were conducted following the end of quantitative fieldwork to gain a richer understanding of the patient experience with the Cytosponge test. Prior to the interviews, the evaluation team and the NHSE team agreed upon themes from the survey results to further explore. The interviews were based on an interview guide to ensure all themes were covered during the one-hour interview slot.

The interview objectives included questions to:

- Understand patient preferences compared to any past endoscopy experience.
- Gain details on specific issues around waiting time.
- Highlight factors contributing to acceptability, and any discomfort or pain experienced during the test.
- Understand patient experience regarding results.

Cognitive testing for the interview guide was not necessary as the questions were based on tested survey items.

Survey respondents were asked if they would like to participate in a follow-up interview. The evaluation team invited patients who consented and provided contact details to arrange a discussion by either phone or Microsoft Teams, which was led by an evaluation team researcher. 28 Cytosponge test patient interviews were completed.

A purposeful sampling approach was applied to respondent recruitment across age, gender, ethnicity, and trust. However, the sample was limited to 12 trusts across 8 Cancer Alliances and included no minority groups. The sample was also limited to patients who participated in the survey, provided contact details, arranged for an interview, and were able to attend the interview. Due to self-selection and the limited sample, data from the interviews should be interpreted with some degree of caution. The ratio of females was higher to males, (61% female, n=17; 39% male, n=11;), however this proportion was equitable to the survey sample (62% female n=217; 38% male, n=133;) and representative of the broader impact evaluation Cytosponge group (58% female, n=893; 42% male, n=656;). Participants who completed interviews were between 33 and 77 years of age, with an average age of 57 years (25-44 years old 16%; 65-77 24%; 45-64 60%). Two patients interviewed were considered outliers and omitted from analyses. These patients could not recall the purpose they were invited for a Cytosponge test and these were unique experiences which may have affected their responses about acceptability of the test and waiting times. A full breakdown of demographic for patients that completed the survey can be found in Appendix C.

The interviews were scheduled for 60 minutes; however participants took between twenty and seventy minutes depending on the level of detail they felt comfortable with sharing when discussing their experience. Patients were informed of the transcription process both in their informed consent form and verbally at the start of the interview. The interviews were recorded and transcribed upon the participant's consent.

All interviews and data analysis were conducted on secure, encrypted IQVIA devices. Transcriptions were cleansed for personal identifiers and analysed using Nvivo version 12, a software programme designed for qualitative data analysis. Thematic analysis was carried out in line with the process evaluation, and included the following six key phases:

1. *Data familiarisation* – initial reading of the interview notes and transcriptions.
2. *Generating initial codes* – initial comments and codes are identified.
3. *Searching for themes* – initial codes are grouped to highlight commonalities between them.
4. *Reviewing themes* – codes and themes are cross referenced with other team members.
5. *Defining and naming themes* – theme names are refined and finalised.
6. *Production of the final report* with each theme summarised and quantified.

Impact Evaluation

Purpose

The overarching aim of the Impact Evaluation workstream was to evaluate the real-world impact of Cytosponge on endoscopy demand, patient outcomes, treatment pathways, and health inequalities in secondary care, using epidemiological and statistical techniques.

NHSE piloted Cytosponge as a triaging pathway in secondary care to help reduce waiting list sizes for endoscopies. Because of this, patients were offered Cytosponge to meet service need, and not through randomisation. The Impact Evaluation, therefore, employed epidemiological and statistical methods to attempt to mimic the conditions of randomisation, determine the impact of Cytosponge on patients who received the intervention (i.e., Cytosponge), and attribute to the intervention measured differences between patients who received Cytosponge and those who did not.

Methodology

Defining the study population

Cytosponge (test) Group: The Impact Evaluation was conducted in the population of patients who were referred for endoscopy in secondary care by their general practitioner between 1st April 2020 and 31st March 2022, were on the waiting list at pilot sites during the inclusion assessment window (1st February 2021 to 31st March 2022), and were offered a Cytosponge test.

Sites determined which patients would undergo the Cytosponge triage based on two factors: (i) the length of time patients had been on the waiting list, prioritising those who had been waiting the longest; and (ii) the number of Cytosponge tests allocated to the site in relation to the total number of patients on their waiting list. Eligibility for these patients was based on data collected on the Cytosponge triage forms during the triage process.

The definition of the test group followed an “intention to treat” approach, including all patients who were offered the procedure, regardless of whether they accepted the procedure or attended the Cytosponge appointment.

Counterfactual (control) Group: In the absence of a randomised control group, the evaluation team had to define an appropriate counterfactual group of patients not receiving a Cytosponge in order to draw conclusions about comparative effectiveness. This counterfactual group (or ‘endoscopy-only group’) was established from the population of patients who were not offered Cytosponge triage during the inclusion assessment window but would otherwise have been eligible to receive it. Primarily, this group came from the cohort of patients who were on the endoscopy waiting list from 1st February 2021 and were referred between 1st April 2020 and 31st March 2022. Of note, only sites that had eligible patients on their waiting list who were not offered a Cytosponge test and sites that started implementing Cytosponge later in the pilot window were able to submit data for the counterfactual group (i.e., these were sites including patients eligible during the start of the pilot who were not offered a Cytosponge because Cytosponge testing had not yet started at the site).

All patients were followed up until 30th June 2022.

Propensity score (PS) weighting

For the comparative analysis, propensity score (PS) matching was initially considered as an effective method to control for measured and unmeasured confounding, while also providing a straightforward method for indexing the counterfactual patients. However, because the number of participants in the counterfactual group was lower than expected, the minimum required sample size (500 patients) was not reached. PS matching was not, therefore, the optimal methodology to control for potential confounding factors whilst retaining study power.

PS weighting was a viable and validated alternative to account for confounding bias in this study and made the best use of all available data, as all eligible patients could be included in the analysis.

Through PS weighting, patients are assigned weights in the analysis so that the weighted sample is balanced in baseline characteristics between the test and control groups, making them more comparable. The final covariates included in the PS regression model used to derive weights for each patient were: age (continuous), sex (male, female), time between referral and index (continuous), ethnicity (white, non-white), indices of multiple deprivation (IMD) divided into five quintiles (1 = most deprived quintile, 5 = least deprived quintile), and calendar time of referral (pre-2021, Q1 2021, Q2 2021, Q3 2021, Q4 2021, Q1 2022).

All descriptive analyses, and those only involving Cytosponge patients, were conducted on the full unweighted cohorts. Comparative analyses were conducted on the weighted cohorts of Cytosponge and counterfactual patients. Note that sample sizes based on results from the weighted comparative analyses are only described using proportions of patients but not counts. This is because the PS weighting methodology produces a weighted cohort, where totals represent the sum of weights, rather than the actual numbers of patients observed in the data, and therefore totals from the weighted cohort do not provide meaningful information.

Pseudo-indexing methodology

The index date used in the weighted comparative analysis of diagnostic waiting times was the date of triage for Cytosponge patients. For valid comparisons of waiting times, counterfactual patients must be similar to Cytosponge patients in terms of the time accrued from diagnosis to being triaged for Cytosponge (or potential to be triaged, in the case of the counterfactual group). Therefore, the index date for patients in the counterfactual group was based upon the distribution of the time from referral to index date within the Cytosponge patients: for each counterfactual patient, an index date was selected and assigned at random from this distribution. Hence, the overall distribution of index dates (relative to referral dates) in the counterfactual group was aligned with that of the Cytosponge patients and the risk of immortal time bias was minimised.

Sample size

Following data cleaning, data from 21 sites that submitted full data for Cytosponge patients (including endoscopy data) was used to build the test group. In the final unweighted cohort, there were 1,549 test patients; the weighted test cohort included 1,338 of these patients (exclusions due to missing IMD and/or ethnicity data used in the PS model). Data from 10 sites that submitted counterfactual data was used to build the counterfactual group. In the final weighted counterfactual cohort, there were 289 counterfactual patients.

The inclusion and exclusion criteria and attrition steps applied for both the Cytosponge and counterfactual groups are in accordance with the statistical analysis plan.

Statistical methodology

The Statistical Analysis Plan (SAP) outlined how the analysis would be conducted to address each objective. In all descriptive analyses, continuous variables were described by the mean, standard deviation (SD), median, first and third quartiles (Interquartile range [IQR]: Q1, Q3), and the minimum and maximum values. Categorical variables were described using number and percent of patients within each category. The number of patients with missing data for each variable was reported where applicable.

Continuous outcomes were described by (weighted) means and (if relevant) 95% CI (or median and interquartile range for skewed variables). Binary/categorical outcomes were described by (weighted) proportions and (if relevant) 95% CI. Comparisons of binary outcomes between the weighted Cytosponge and counterfactual groups were made through logistic regression.

Time to event outcomes were evaluated using Kaplan-Meier methods. Patients were followed until the end of their diagnostic pathway, defined as the latest of their date of endoscopy or date of a negative Cytosponge test result. Hence, for Cytosponge patients with a negative test result who were not referred for a subsequent endoscopy, the end of their diagnostic pathway was the date of their negative test result. For all other patients (counterfactual patients, Cytosponge patients with a non-negative test result, and Cytosponge patients with a negative test result who were referred for a subsequent endoscopy), the end of their diagnostic pathway was their date of endoscopy.

The median time-to-event was described along with 95% CI, and Kaplan-Meier survival curves were inspected graphically for the Cytosponge and counterfactual groups. Comparisons of time to event outcomes between the weighted Cytosponge and counterfactual groups were made through Cox regression. For patients in the weighted Cytosponge and counterfactual groups, analyses of time to diagnosis or confirmed test result were additionally stratified according to the time period within which patients were indexed during the pilot scheme. For patients in the Cytosponge group, prior to PS weighting, time to event outcomes were presented pre/post the Cytosponge test, stratified according to the action taken as a result of the Cytosponge test. Additionally, the time to BO diagnosis or confirmed result was presented stratified by both the test result and subsequent action for both the unweighted and weighted cohorts of test patients.

To explore possible health inequalities in the Cytosponge pilot, firstly, the demographic characteristics of Cytosponge and counterfactual patients were analysed (i.e., sex, age, ethnicity, and IMD). Secondly, the test results and subsequent actions of the unweighted Cytosponge group were stratified by demographic characteristics to explore potential inequalities in access to a diagnosis. Lastly, the time to a BO diagnosis or confirmed test result date and rates of endoscopy in the weighted Cytosponge and counterfactual groups were stratified by IMD quintile and ethnic group to explore potential inequalities in patient outcomes.

Limitations of the analysis

(i) Hidden bias / confounding

Since patients were not allocated to the Cytosponge and counterfactual groups at random due to the real-world nature of the pilot programme, there was the potential for a lack of comparability between the two groups due to confounding bias (i.e., presence of factors other than the intervention leading to differences in patient outcomes). To mitigate this, patients in both groups were weighted based on baseline characteristics to be more similar to each other. However, the weighting methodology did not account for all health-related factors, such as comorbidities, that could affect the outcomes of patients as this data was not available. Hence, unmeasured confounding bias cannot be ruled out.

Eligibility for counterfactual patients was determined by individual sites, and it was assumed that the patients who contributed to this group met all the required eligibility criteria. A summary of the methodology and triaging criteria applied by each site to select counterfactual patients is included in the SAP. Of note, the information provided by sites highlights some variations in the methodology and criteria applied by sites (e.g., the approach used to identify the primary diagnosis and procedure of the patients). This may result in the prevalence of patient outcomes for counterfactual patients to be overestimated, for instance, if the counterfactual patients were more likely to have conditions that would have made them ineligible for Cytosponge or increased their risk of BO.

Patients in the counterfactual group were primarily selected according to symptoms recorded at the time of endoscopy, and it is possible only more severe symptoms were recorded. This means those in the counterfactual group may be more unwell, and hence more likely to have BO, other adverse outcomes, or shorter waiting times compared to the Cytosponge group. This would lead to Cytosponge appearing to miss more BO diagnoses than is truly the case or increasing diagnostic waiting times.

Furthermore, patients in the counterfactual group were drawn from those who had an endoscopy (a subset of the entire pool of patients referred for endoscopy), implying that they must have survived from their index date up until their date of endoscopy. This introduces the potential for immortal time bias, but this is likely to be small given that the included patients had low risk symptoms and were required to have a minimum of three months follow-up. However, this is considered as a limitation of this study, conferring a spurious advantage to the counterfactual group in terms of time to event outcomes.

(ii) Selection bias

Selection bias may be present in the Cytosponge group, given evidence that sites typically submitted data for patients who accepted Cytosponge, rather than all those who were offered it. Bias would be introduced if those willing to accept the procedure were systematically different from those who did not. The extent and direction of this bias are unknown, but for example, if patients with more severe symptoms who are at higher risk of BO or other adverse outcomes were more likely to accept the test, Cytosponge may then appear to lengthen waiting times more than is truly the case. This is because patients with more severe symptoms would be more likely to be referred for subsequent endoscopy after a Cytosponge test and may therefore exit the pathway later than those with less severe symptoms who were discharged.

Sites contributing data were located across England but were typically located in more sub-urban environments and outside the North-East. Counterfactual data did not have such a wide coverage of England as the Cytosponge data. This was a limitation, and these sites may not be representative of the wider population of England.

Furthermore, differences in the methodology and criteria applied by sites to select the counterfactual group might have also impacted the broader representativeness of this group.

(iii) Information bias

Data was collected retrospectively from medical records for the patients in the counterfactual group, as well as some endoscopy and clinical outcomes data for the Cytosponge group, which was limited by the completeness and accuracy of the underlying information. Data that was not recorded in the Cytosponge evaluation dataset or endoscopy system datasets, that was miscoded in these datasets, or that failed to accurately describe clinical treatments all have the potential to introduce bias.

Furthermore, it was not possible to determine with certainty when the end of the diagnostic pathway was reached for a small proportion of Cytosponge patients (i.e., around 15%). This would have the effect of lengthening the observed time Cytosponge patients waited to exit the diagnostic pathway and therefore bias the overall results, since the end of the pathway was fully observed for the counterfactual patients.

The date of BO diagnosis and end of the diagnostic pathway was assumed to be the same as the date of endoscopy in both groups, due to a lack of information provided by the sites on the date of endoscopy result in the cases where pathology samples were taken. Hence, the overall time patients waited until receiving a definitive diagnosis will be underestimated for some patients in both the Cytosponge and counterfactual groups. Waiting times may be more likely to be underestimated for counterfactual patients due to the larger proportion of patients undergoing endoscopy, with the opportunity for pathology samples to be taken, in this group.

(iv) Other potential biases

Counterfactual patients were pseudo-indexed based on the distribution of time between referral and triage amongst the test patients. This approach assumes that triage dates occur at random in the test patients relative to their referral date. This assumption may not have been met, especially if there were patient characteristics which influenced time of triage relative to referral date (e.g., if some patients were difficult to get hold of for triaging).

Health Economic Evaluation

Purpose

The Economic Evaluation workstream used economic modelling techniques to estimate the cost-effectiveness and budget impact of implementing Cytosponge as a routine referral triaging tool for low-risk GORD patients waiting for an endoscopy. The analysis considered the perspective of the NHS and assessed the impact on waiting times, avoided endoscopies, and the detection rate of Barrett's oesophagus (BO). The findings also informed an estimate of the financial investment required for a national roll-out of Cytosponge in this context.

Methodology

The following is a summary of the methodology behind the cost-effectiveness model (CEM) and budget-impact model (BIM) used for health economic analysis. Some key definitions are provided, and the model structures, key inputs and assumptions, and outputs are described.

Key definitions

Cost-effectiveness

Cost effectiveness is determined by the National Institute for Health and Care Excellence (NICE) using the Incremental Cost-Effectiveness Ratio (ICER). This ICER is a ratio of the difference in costs to the difference in Quality Adjusted Life Years (QALYs) for an intervention (the Cytosponge program) relative to an incumbent programme (Endoscopy-only programme) (NICE, 2012).This ICER is a ratio of the difference in costs to the difference in Quality Adjusted Life Years (QALYs) for an intervention (the Cytosponge program) relative to an incumbent programme (Endoscopy-only programme) (NICE, 2012).

To assess cost-effectiveness, the ICER is compared to a willingness-to-pay (WTP) threshold, which is the maximum price a payer is willing to pay for an additional unit of QALY gain. NICE's WTP threshold range is £20,000 - £30,000.

The Net Monetary Benefit (NMB) is a useful statistic alongside the ICER. It calculates the incremental QALYs in monetary terms based on the WTP threshold and subtracts the incremental cost. A positive NMB indicates a cost-effective outcome, while a negative NMB suggests otherwise. The NMB provides a single scale to express the ICER and evaluate uncertainty in the cost-effectiveness statistic.

Budget-impact

A budget impact test assesses the short-term affordability of interventions considering a cohort who are eligible for ‘treatment’ with the intervention (e.g., Cytosponge) – rather than only a per-patient estimate of cost-effectiveness. With respect to NICE standards, the budget impact is the estimated additional cost to the NHSE budget over three years if the intervention is introduced into the healthcare system on a national scale (i.e., in England) and offered to the entire eligible population. There is no measure of health benefit in a budget impact assessment; it is simply an assessment of costs – although cost savings/increases resulting from health effects may be realised.

Direct medical costs

These are the costs directly attributable to patient care. In this context this includes: the acquisition costs of diagnostic tools and medical treatment, the cost of administering treatment/diagnosis (e.g., nurse time, the cost of inpatient care), and the costs of treatment-related adverse events.

Arms

In the CEM the alternate arms are referred to as “Cytosponge arm”/“Cytosponge pilot programme” and “Endoscopy-only arm”/”Endoscopy-only programme”.

Model development

Cost-Effectiveness Model (CEM)

A cost-effectiveness model (CEM) was developed using Microsoft® Excel® to evaluate the direct medical costs and benefits of diagnosis and treatment for patients in England from a NHSE perspective, using a lifetime time horizon. The costs were measured in pounds sterling, and the benefits were measured in quality-adjusted life years (QALYs).

The CEM was structured as a Markov model, consisting of discrete cycles representing constant time intervals. Patients could transition between different health states throughout the cycles, including No Barrett's oesophagus (No BO), non-dysplastic Barrett's oesophagus (NDBO), low-grade dysplasia (LGD), high-grade dysplasia (HGD), oesophageal adenocarcinoma (OAC), and death. The model structure was based on previous Markov models found in the literature, and health states were associated with specific costs and QALYs per cycle (Benaglia et al., 2013; Sami et al., 2021).

Movement between health states occurred at the end of each cycle based on transition probabilities sourced from published literature(Sami et al., 2021). The speed of movement through health states depended on the diagnostic pathway being evaluated. The costs and QALYs were aggregated within each cycle by multiplying the probability of being in each health state by its specific cost and QALY values. The total costs and QALYs were then aggregated over all cycles to calculate the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB).

The CEM consisted of two distinct phases. Phase 1 represented the short-term diagnostic pathway, which included the waiting time for an endoscopy and the time until the final test result. This phase had three non-constant cycles defined by specific milestones. Patients in the Cytosponge arm were stratified based on Cytosponge test results and subsequent actions, and transition probabilities varied depending on the subgroup. Phase 2 represented the post-diagnostic lifetime pathway, assuming constant annual cycles. During this phase, all patients underwent appropriate monitoring and surveillance based on their health state.

The base case analysis used patient baseline characteristics from the Impact Evaluation workstream. In the Cytosponge arm, patients were divided into subgroups based on test results and subsequent actions. A median time to diagnosis was applied to each subgroup. The Endoscopy-only arm had a median time to diagnosis for the entire sample: 46 days, based on a median time from referral-to index of 18 days, and a median time from index to diagnosis of 28 days, estimated in the Impact Evaluation. Of note, the median time-to-diagnosis in the Endoscopy-only arm was less than the median time from referral to diagnosis for the entire Cytosponge arm using either unweighted (82 days) or weighted (75 days) data. In scenario analyses, alternate (longer) time-to-diagnosis values in the Endoscopy-only arm were considered (i.e. 73.8 days, and 126 days, reflecting the longest waiting time during the COVID-19 pandemic and the maximum time within which patients must be treated according to the NHS constitution).

The sensitivity in the Cytosponge arm was based on the BEST2 study (79.9%) while the sensitivity in the endoscopy-only arm was assumed to be 100% (Ross-Innes et al., 2015). Of note, while in reality endoscopies are not 100% sensitive, this simplifying assumption was considered appropriate for establishing the difference in test accuracy across programmes since an endoscopy was considered the gold standard confirmatory test in the Cytosponge arm. Furthermore, clinicians typically will not re-order an endoscopic investigation when a patient had a recent endoscopy with negative results. Effectively the analysis considered endoscopy-detectable BO across arms. The same assumption was made in previous analyses (Benaglia et al., 2013; Swart et al., 2021).

The resources associated with Cytosponge testing were based on those used in the pilot programme: this included the Cytosponge device and subsequent pathology, nurse administration time, and a non-consultant led outpatient appointment. The costs of these resources were based on published data from the NHS, NICE and PSSRU (NICE, 2020). The cost of endoscopy testing included a health resource group (HRG) cost from the latest national schedule of NHS costs (2020/21) and the cost of an additional non-consultant led outpatient attendance (NHSE England, 2022). The HRG used was FE21Z (Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures with Biopsy, 19 years and over) and accounted for devices (e.g., endoscope) and subsequent pathology, nursing and consultants required for conducting endoscopy, and ward costs (including ward nursing and indirect clinical costs).

Health states, and associated utilities and costs used in the analysis were based on previous studies. Health state costs included treatment costs for Barrett's oesophagus and oesophageal adenocarcinoma, while utilities captured the quality of life associated with each health state.

The CEM allowed for the evaluation of short-term and long-term costs and QALYs, providing insights into the cost-effectiveness of the diagnostic pathways. It followed NICE guidance and could be modified into a cost-comparison model if equal efficacy was assumed. Sensitivity analyses were conducted to test the impact of different data sources and assumptions on the results (NICE, 2012)

For a full list of the inputs, sources, assumptions, and alternate scenarios, included in the analysis please refer to the Economic Evaluation technical report.

A summary of some of the key base-case settings, inputs and assumptions are presented in Table 2

Table 2: Base-case settings and assumptions

Model parameter	Base case settings and assumptions	
	CEM	BIM
Mean age at entrance to the model	52	
Percentage of the population male:	42.4%	
Completion rate for Cytosponge	93%	
Sensitivity of Endoscopy	100%	
Sensitivity of Cytosponge	79.9%	
Specificity of Cytosponge	92.4%	
Median time-to-diagnosis (Endoscopy-only arm)	46	
Assumptions regarding protocol adherence	Based on observed outcomes (not strict adherence)	
Probability of false negative patients re-presenting in secondary care within diagnostic pathway	100%	
Included costs	Direct costs: diagnostic test acquisition and administration costs, subsequent treatment acquisition and administration, and adverse event costs	
Nurse band: Cytosponge	Band 7	
Nurse band: Endoscopy	Band 7	
Method for counting number of completed endoscopies	Exclude censored patients (assume censored patients do not have an endoscopy and are therefore discharged).	
Diagnostic pathway (phase 1) time horizon	150 days	
Starting eligible incident population size year 1	N/A	15,121
Service provision share (Cytosponge)	N/A	Lower bound: Initial share, 10%; increasing at 10% annually Upper bound: Initial share, 90%; increasing at 10% annually
Annual rate of increase in incidence	N/A	3% annually
Time horizon	48 years (lifetime)	5 years

Budget Impact Model (BIM)

The budget impact model (BIM) was also developed in Microsoft® Excel®. The aim was to capture the direct medical costs (in pounds sterling) accrued both annually and cumulatively over a five-year period, post introduction of Cytosponge in this use case and patient context within the NHS in England. The BIM made use of per-patient annual costs produced in the CEM, and so BIM results were indirectly functions of the CEM inputs that generated the annual costs in the CEM (namely, direct medical costs, survival [transition probability], and mortality inputs).

Model structure

The BIM considered two scenarios: the 'world with Cytosponge' (WWC) and the 'world without Cytosponge' (WWoC). In WWoC, costs were projected based on the current service provision mix, where eligible patients were referred to routine endoscopy without Cytosponge triage. In WWC, the service provision mix was updated annually to increase the proportion of eligible patients placed on the Cytosponge programme.

The model estimated the incident population of eligible patients in each year, which remained the same in both worlds. The prevalent population, adjusted for survival, was also estimated for each year. Incident patients entered the waiting list and diagnostic pathway in their year of incidence, while subsequent years focused on monitoring costs.

Annual costs were applied to each patient in each year based on the specific programme they were assigned to. In WWC, the cost depended on the share of patients assigned to the Cytosponge programme. Monitoring costs were included in all years beyond the first year.

For patients incident in year 2, a larger proportion were assigned to the Cytosponge programme in WWC than in year 1. This pattern continued throughout the time horizon, with an increase of 10 percentage points in the share of incident patients assigned to the Cytosponge programme every year.

The budget impact analysis calculated the annual difference in costs between WWC and WWoC and aggregated them to represent the net budget over five years. A range of results were computed to account for varying service provision mix assumptions.

In the BIM, the cost directly attributable to the diagnostic pathway in year 1 of WWC was used as a proxy for the potential cost of national Cytosponge roll-out in England. However, this value only accounted for direct medical costs and not investment costs (namely, the costs related to any required additional clinic set up, initial training and education costs, initial costs of raising awareness).

Key inputs for the BIM included epidemiology inputs to estimate the incident eligible population and the annual rate of increase in the incident population. The eligible incident population was estimated using data from the pilot programme and the NHSE monthly diagnostics procedure database (NHS England, 2022b)

Due to the lack of evidence-based forecasts of the service provision mix, a range of budget impact results were generated by assuming different initial and subsequent shares assigned to the Cytosponge program.

Please refer to the Economic Evaluation technical report for more details on the model structure, inputs, and assumptions. Model outputs are summarised below in Table 3.

Table 3 CEM and BIM model outputs

CEM	BIM
The total life years (LYs), QALYs, and costs in both arms	The annual and cumulative overall cost in each world
The disaggregated (by health state, and phase) QALYs, and disaggregated (by cost category, and phase) costs	The annual and cumulative budget impact
The incremental LYs, QALYs, and costs relative to the endoscopy-only programme.	The disaggregated (by cost category, and phase) annual and cumulative costs
The ICER and NMB	

Sensitivity analyses in the models included one way sensitivity analyses (OWSA) and scenario analyses to test robustness against alternative assumptions. OWSA involved modifying a single parameter while holding others fixed to assess its impact on the overall outcome. Scenario analyses evaluated the effect of different assumptions on model results. Key alternate scenarios tested included equal efficacy, variations on pathway implementation and optimal protocol adherence (i.e., no variations), using weighted comparative analysis outputs, and assuming no return of false negative patients to secondary care.

Please refer to the Economic Evaluation technical report for a full list of scenarios tested, and the variables tested in the OWSA.

A probabilistic sensitivity analysis (PSA) was conducted in the CEM to evaluate uncertainty in the ICER. Parameters were simultaneously varied over multiple iterations, sampled from probability distributions. The PSA provided confidence estimates by analysing the proportion of PSA ICER results within specific WTP thresholds. Although limitations existed regarding joint uncertainty and variable correlations, PSAs are commonly used to assess uncertainty in cost-effectiveness.

Model limitations

The CEM and BIM used in the analysis have certain limitations and uncertainties that should be considered when interpreting the results.

(i) Inherent limitations due to pilot programme data

The short-term phase 1 analysis relied on findings from the Impact Evaluation, which potentially introduced limitations such as confounding bias, selection bias, information bias, and triaging bias. The reduced sample size in the counterfactual arm required a propensity score weighting approach, which has its own challenges and potential bias. Variations in how the patient diagnostic pathway clinical guidance was implemented also affected the results. Please refer to the limitations section in the Impact Evaluation for an overview.

(ii) Data availability for key parameter values

There were uncertainties in key parameter values. For example the sensitivity and specificity inputs were based on the BEST2 trial (Swart et al., 2021): a different use case. Furthermore, there were uncertainties in the health state utility values (taken from the analysis by Swart et al; not based on directly elicited values from patient reports), and transition probabilities considered (taken from the analysis by Swart et al who discuss the lack of available data requisite to provide reliable base case estimate of transitions to/from certain health states – e.g., transitions between OAC and death). In response, where possible, values were chosen that were biased against Cytosponge, higher and lower values were considered in sensitivity analyses, and/or alternate parameter values based on alternate data sources were considered in scenario analyses.

(ii) Data availability BIM specific parameter values

The key limitations mentioned above were shared both by the CEM and BIM (except for issues surrounding utility values which do not affect the BIM). However, the main limitation of the BIM was the lack of evidence regarding service provision mix assumptions. In response, several different scenario values were tested and a range of results reported rather than a point estimate. It is recommended to update the BIM with new evidence and real-world data as it becomes available during the technology's roll-out.

Impacts of COVID-19 on healthcare services and the evaluation

The COVID-19 pandemic created additional challenges in access to healthcare and affected demand for services. The evaluation findings should be considered within this context.

The Cytosponge pilot took place during the period of the COVID-19 pandemic, during which there were additional challenges in access to and provision of healthcare services. The time period for the evaluation is therefore not representative of usual (previous) healthcare context. This needs to be borne in mind when considering the findings across evaluation workstreams.

For instance, rates of referrals and appointments might have been lower during the COVID-19 pandemic compared to before the pandemic, potentially affecting numbers of patients and waiting times. Patients were also required to provide a negative COVID-19 test before attending a clinic. This increased the administrative burden on clinics, especially when a patient presented without a COVID-19 test result and was required to book a new clinical appointment. This factor may have increased the apparent difficulty of booking an appointment for endoscopy and/or Cytosponge in some cases. It may also have had an impact on the administrative demands placed on staff in clinical roles.

Further, some Cytosponge clinics were in areas of hospitals that had limits on the number of health care professionals (HCPs) and patients (to allow for social distancing). In some cases, these areas were endoscopy units, which impacted the potential number of patients able to visit the unit at any one time and overall. Depending on the urgency of referral (e.g., whether they were classified as “routine reflux” or urgent) and individual circumstances of the patient, this factor may have increased the difficulty of booking an endoscopy unit appointment. Because appointment times and, subsequently, waitlist times for Cytosponge were shorter than those for endoscopy, this may also have increased the demand for Cytosponge (i.e., more Cytosponge patients could be attended to within a given day than endoscopy patients).

Overview of data sources used in the evaluation

Data sources used in the evaluation report are outlined below with relevant caveats and limitations highlighted.

Table 4 Qualitative data sources description and limitations

Evidence source	Description	Caveats and limitations
Process Evaluation stakeholder engagement	Insights gathered via semi-structured interviews (site and programme level); site level workshops; and open insight workshops delivering Cytosponge services.	The deep dive at site level was carried out in six sites. The selection of these sites aimed to ensure they were as representative of all pilot sites as possible. However, due to heterogeneity across pilot sites, not all findings can relate across all sites. Also, reflective of a barrier identified, not all sites had an engaged senior clinician and therefore their insight was inferred from those who were interviewed at their particular sites.

Evidence source	Description	Caveats and limitations
Patient survey	Results from multiple choice surveys sent to patients who completed the Cytosponge test.	Patient survey results collected in the Patient Experience workstream should be interpreted with caution due to the self-reported nature of the survey and sample (n=357 of >2,000 patients who participated in the pilot across 14 NHS Trusts). The sample was limited to patients who provided a valid e-mail address and had internet access. The response rate of 26% (352 responses from 1,351 invitations) ensures a 95% confidence interval and 5% margin of error. Responses >340 are expected to yield a statistically significant data set. Statistical significance testing was carried out on the following core variables: differences between males and females; difference in people who have had an endoscopy before vs. people who have not; people who had a follow-up endoscopy after Cytosponge vs those who were discharged.
1:1 patient interviews	Further details on patient experience were collected by inviting patients who completed the patient experience survey and consented to be contacted for a follow-up discussion to complete an interview.	The sample of patients invited to be interviewed was limited to those who completed the Patient Experience survey, consented to be contacted for follow-up, provided valid contact details, responded to requests for interviews, and attended the interview (n=28). Those who completed the latter consisted only of patients who accepted the offer of the Cytosponge test and were not from minority-backgrounds. Additionally, not all sites that participated in the survey are represented, and those that are, are not equally proportional due to the self-selective nature of patients choosing to participate in the interviews. Two patients interviewed were considered outliers and omitted from analyses. These patients could not recall the purpose they were invited for a Cytosponge test and these were unique experiences which may have affected their responses about acceptability of the test and waiting.

Table 5 Quantitative data sources description and limitations

Evidence	Description	Time period	Number of patients and sites	Caveats and limitations
Management Information (MI) data	Management information data is an aggregate dataset completed by Trusts and collected by NHSE on a monthly basis. Sites involved in the Cytosponge evaluation are asked to provide data on the number of Cytosponges completed, number of adverse events, number of patients discharged, number of patients referred for endoscopy, and number of BO or cancer diagnoses. This information informs how Cytosponge is being implemented across the pilot sites.	February 2021 – April 2022	2170 Cytosponge procedures confirmed out of 2875 patients invited to receive a test. 23 sites.	The number of sites submitting management returns data to NHSE is not inclusive of the total number of sites in the pilot. Sites with missing management returns data (due to either no or very low numbers of Cytosponge patients during the evaluation period) include Calderdale and Huddersfield NHS Trust, Lancashire Teaching Hospital NHS FT, University Hospitals Dorset, York Teaching Hospital NHS FT, Hull Teaching Hospital NHS FT, Guys and St Thomas NHS FT.
Cyted pathology data	Cyted is a third-party company that is responsible for the pathology analysis of the Cytosponge tests. Cyted contains data on every patient that received a Cytosponge test at participating sites.	February 2021 – March 2022	1846 Cytosponge results processed (inclusive of an unknown number of repeat Cytosponge procedures) 29 sites.	The diagnosis pathway and further actions following pathology results are not provided within this dataset and cannot be linked to other data sets due to patient all identifiable data being removed. Total number of repeat Cytosponge procedures within the dataset has not been confirmed. This dataset was not quality checked for the presence of comorbidities and

Evidence	Description	Time period	Number of patients and sites	Caveats and limitations
	This data includes the number of Cytosponges completed and the test outcome data by site.			other exclusion criteria for Cytosponge.
Impact Evaluation analysis (Cytosponge group)	All sites were asked to complete three forms (triage, appointment, and results forms) to collect data on patients with low-risk reflux symptoms who have been referred for endoscopy and were offered a Cytosponge test. Each site shared patient level data from these forms alongside data on endoscopy outcomes for these patients with IQVIA.	February 2021 – June 2022	2402 Cytosponge forms collected. 1549 eligible patients following attrition. 22 sites.	The Cytosponge patient cohort only captures patients who were eligible for Cytosponge after applying the inclusion and exclusion criteria based on their medical history and the type and date of endoscopy referral (final sample size = 1,549).
Impact Evaluation analysis (counterfactual group)	This group was established from the population of patients who were not offered Cytosponge triage during the inclusion assessment window but would otherwise have been eligible to receive it. Each site shared patient level data on endoscopy outcomes for these patients with IQVIA.	February 2021 - June 2022	1392 patients with counterfactual data. 289 eligible patients following attrition. 10 sites.	There were variations in the methodology and criteria used by sites to identify counterfactual patients, which might have introduced confounding and selection bias. Furthermore, counterfactual patients were primarily selected according to symptoms recorded at the time of endoscopy, so only more severe symptoms might have been recorded.
NHS national statistics	Monthly estimates of the number of patients waiting longer than 6-weeks for endoscopy.	March 2021 – March 2022	22 sites.	These are publicly available datasets that record waitlist times for all NHS hospitals. There may be additional factors that impact the waitlist times that are unrelated to Cytosponge.

Table 6: Health Economic Evaluation quantitative data sources description and limitations

Data	Description	Limitations
BEST 2 Trial	Multicentre cohort study (BEST2), patients with Barrett's oesophagus underwent the Cytosponge test before their surveillance endoscopy. Clinical and demographic data was collected and informed both sensitivity and specificity inputs for the Cytosponge which were used in the model.	The sensitivity and specificity values in the BEST2 analysis were in a different use-case (primary care screening tool) so are not completely accurate to this analyses use-case.
Economic evaluation of Cytosponge®-trefoil factor 3 for Barrett oesophagus: A cost-utility analysis of randomised controlled trial data (Swart et al, 2021)	The phase II Markov model was modelled based on the design of the cost-utility model in Swart et al, 2021. The majority of inputs were taken directly from this analysis including health-state transition probabilities, treatment related transition probabilities, the proportion of patients receiving different treatment options, type and incidence of adverse events, annual utilities and annual disutilities.	N/A
Impact Evaluation analysis (counterfactual group)	As above.	As above.
Impact Evaluation analysis (Cytosponge group)	As above.	As above.

Data	Description	Limitations
KOL validation (a gastrologist, two Cytosponge nurses, and two NHS finance experts)	Interviewed to confirm inputs including impact of current endoscopy waiting times on disease prognosis, resources used in both pathways, and descriptions of patient pathways.	Resource use and endoscopy waiting times vary considerably between sites and therefore the findings of KOLs could vary considerably depending on where there are based.
Multiple literature sources (see technical report for full individual details)	Several specific inputs were sources from the literature when more appropriate alternatives could not be identified.	N/A
National Schedule of NHS costs 2021-2022	The National Cost Collection publication comprises aggregated costs (the average unit cost of providing defined services to NHS patients in England) and patient-level costs (a cost based on the specific interactions a patient has, and the events related to their healthcare activity).	N/A
NHSE Monthly Diagnostics Waiting times and Activity	The monthly diagnostics collection collects data on waiting times and activity for 15 key diagnostic tests and procedures.	These are publicly available datasets that record diagnostic test activity for all NHS hospitals. The data may have been biased by hospital recovery lag following COVID-19.
NICE Clinical guideline [CG106]	NICE. Barrett's oesophagus - ablative therapy (CG 106) Appendix 6: cost-effectiveness analysis for Barrett's Oesophagus. 2010.	N/A
NICE Clinical guideline [CG184]	Appendix A: Dosage information on proton pump inhibitors.	N/A
NICE MedTech innovation briefing MIB240	NICE developed a MedTech Innovation Briefing (MIB) on Cytosponge for detecting abnormal cells in the oesophagus and included the unit cost for a Cytosponge device and protocol for the device's usage.	N/A
ONS National population projections: 2020-based interim (release date: 12 January 2022)	Total population of ≥ 18 years old in England by year.	N/A
ONS National population statistics life tables 2018-2020	Period life expectancy by age and sex for the UK. Each national life table is based on population estimates, births and deaths for a period of three consecutive years. Tables are published annually.	A cohort modelled from the years 2022-2026 (BIM) or 2022-2070 (CEM) uses probabilities of survival taken from a population sample from 2018-2020.
Personal Social Services Research Unit. Unit Costs of Health and Social Care 2021. 2021.	Annual unit costs for hospital services as well as community health care and social care services. The volume is made available online in December each year.	N/A

Abbreviations: BIM: Budget Impact Model; CEM: Cost effectiveness model; CG: Clinical guideline; KOLs; MIB: Medical Innovation Briefing; N/A: Not applicable; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; ONS: Office for National Statistics

SECTION 3: SUMMARY OF EVALUATION FINDINGS

This section presents the key findings for each evaluation question using data and analysis from the relevant workstreams.

Evaluation Question 1: Endoscopy demand

What impact does Cytosponge (delivered in secondary care as a routine referral triaging tool) have on endoscopy demand?

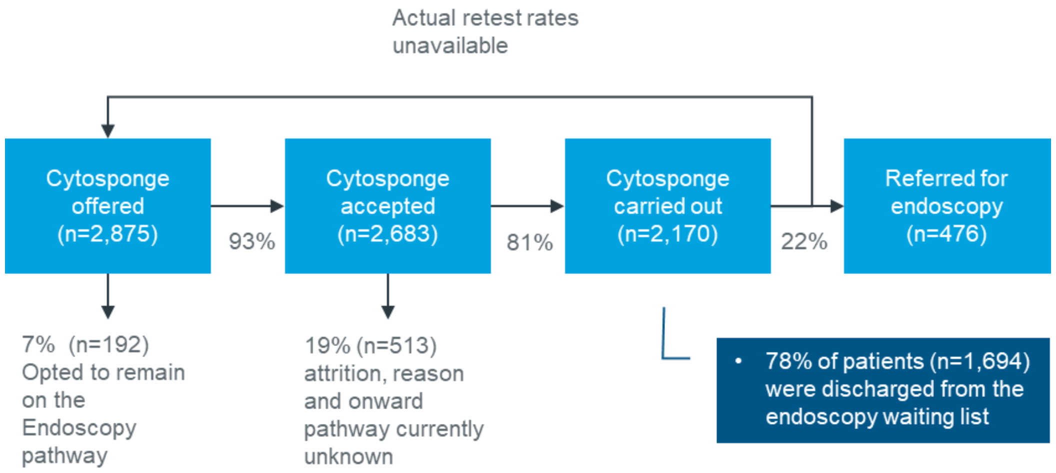
The analysis and findings on the effectiveness of Cytosponge in reducing endoscopy demand are based on evidence drawn from the Management Information (MI), Impact Evaluation and Cyted datasets. This is supported by and triangulated against evidence from the Process Evaluation (e.g., particularly regarding variations in how the recommended Cytosponge pathway guidance was followed).

Cytosponge testing effectively reduced endoscopy demand in secondary care by 78% in patients who completed a Cytosponge test.

Both MI data and Impact Evaluation data show that Cytosponge was an effective tool for reducing the demand for endoscopy for patients with low-risk reflux symptoms referred to secondary care on a routine referral. MI data shows that 78% (n=1,694) of patients who completed a Cytosponge test were discharged or monitored (i.e., removed from the endoscopy waiting list). All these discharged patients would likely have undergone an endoscopy if they had not completed a Cytosponge test, so this represents a substantial reduction in demand for endoscopies immediately after undertaking the test. Comparative analysis from Impact Evaluation data broadly supported this, with 80.7% of patients in the weighted Cytosponge group not having a record of endoscopy. In this data there was some evidence of missing endoscopy information in those who were known to be referred following a Cytosponge test, but assuming all referred patients did indeed complete an endoscopy, there would still be a substantial reduction in endoscopy demand, with approximately 73% of patients avoiding endoscopy. Note that the present pilot did not collect longer-term follow-up data on the outcomes of patients who were removed from the endoscopy waiting list. Hence, it was not possible to determine whether these patients re-presented to secondary care longer-term.

The majority of patients eligible for a Cytosponge test accepted the offer and completed the test. The MI data shows that only 7% of the patients who were offered the Cytosponge procedure did not accept it, and a further 19% (n=513) accepted the offer but did not complete the procedure. There may be a number of reasons for this, including patients not responding to the offer, missed appointments, inability to swallow the sponge, or difficulties accessing the clinics due to COVID-19 related restrictions. Figure 5 presents the flow of patients through the Cytosponge pathway based on MI data (see Appendix A for detailed data by site).

Figure 5. Patient flow through Cytosponge pathway



Source: MI data

There is some evidence that Cytosponge helped to triage patients (both high and low risk), as most BO cases were found on the endoscopy outcomes of patients with positive test results, while no BO cases were detected in patients who had a negative test result but nonetheless underwent an endoscopy.

The Cytosponge clinical guidance states that a patient's diagnostic pathway for onward endoscopy is dependent on the atypia, p53 and TFF3 cytopathology results of their Cytosponge test. Specifically:

- Patients with definite or uncertain atypia and/or abnormal or equivocal p53 results should receive an urgent confirmatory endoscopy.
- Those with negative atypia results and negative p53 but positive TFF3 pathology should be referred for a routine endoscopy.
- Those with inadequate samples may require Cytosponge retest or an endoscopy according to clinical judgement.

MI data indicates that Cytosponge helped to identify higher-risk patients requiring an endoscopy, with 22% of patients who completed a Cytosponge test (n=476 of 2,170) being referred for an endoscopy (Figure 5).

The outcomes of Cytosponge testing observed in the pathology data (Cyted) (Table 7) and the Impact Evaluation data broadly align with the referral rates described above. Based on the Cyted data, 8.7% of Cytosponge tests from patients with reflux symptoms were positive for atypia or TFF3 (1.3% and 7.5% respectively), and 168 tests were uncertain (9.1%). This means that 17.8% of patients had positive or uncertain test results and may have required a confirmatory endoscopy according to the clinical guidance.

Table 7 Results outcomes of Cytosponge amongst patients who successfully completed the test with adequate sample (n=1838)

Results outcomes	Cyted data percentage of patients (%)
Positive	8.7% (n=160)
Atypia Positive	1.3% (n=23)
Atypia Positive + p53 positive	*0.2% (n=4)*
Atypia positive + uncertain significance (TFF3 negative or p53 negative)	*0.8% (n=14)*
Atypia positive + p53 equivocal	*0.3% (n=5)*
TFF3 positive only (*no Atypia positive*)	7.5% (n=137)
Uncertain *	9.1% (n=168)
Atypia results inconclusive	0.1% (n=1)
Insufficient sample results	9.1% (n=167)
Negative *	90.8% (n=1647)
Atypia negative	89.6% (n=1647)

Note that patients considered uncertain may also be counted within the Negative cohort due to negative recordings of Atypia but inconclusive recordings of TFF3 and P53

Source: Cyted data

There is some evidence that Cytosponge could be an effective triaging tool based on endoscopy outcomes of those with a negative Cytosponge test (i.e., no cases of BO were detected in patients who had a negative Cytosponge but nonetheless underwent an endoscopy). Furthermore, most cases of BO were detected amongst patients who had a positive Cytosponge and subsequently received a confirmatory endoscopy. Note that the present pilot was not designed to assess the long-term accuracy of Cytosponge. Hence, further research using longer-term follow-up data would be required to determine its effectiveness beyond the timeframe of this evaluation.

The recommended diagnostic pathway for endoscopy referral was followed for most patients.

The Impact Evaluation data shows that the recommended diagnostic pathway for endoscopy referral following a Cytosponge test was followed in most cases. As expected according to the clinical guidance, the majority of patients with positive or uncertain test results were subsequently referred for an endoscopy, while most patients with negative results were not referred for an onward endoscopy (Table 8).

Across all groups of patients, whether they received positive, negative, or uncertain test results, most onward referrals were made for a routine endoscopy. Urgent referrals were predominantly made for patients with positive test results.

Table 8 Subsequent actions of patients who successfully completed Cytosponge stratified by their test results, (n=1,411)

Patient outcome	**% Of patients referred for an onward endoscopy**				**% Of patients discharged**	**% Of patients referred for repeat test**	**% Of patients with unknown actions**
	Routine	**Urgent**	**Unknown urgency**	**Total**			
Positive 9.1% (n=129)	59.7% (n=77)	17.8% (n=23)	8.5% (n=11)	86% (n=111)	6.2% (n=8)	3.9% (n=5)	3.9% (n=5)
Uncertain 9.1% (n=128)	50% (n=64)	8.6% (n=11)	9.4% (n=12)	68% (n=87)	1.6% (n=2)	15.6% (n=20)	14.8% (n=19)
Negative 75.12% (n=1,060)	5.8% (n=62)	0.9% (n=10)	0.7% (n=7)	7.5% (n=79)	67.1% (n=711)	0.4% (n=4)	25.1% (n=266)
Unknown 6.66% (n=94)	18.1% (n=17)	2.1% (n=2)	11.7% (n=11)	31.9% (n=30)	13.8% (n=13)	1.1% (n=1)	53.2% (n=50)
Total 100% (n=1,411)	15.6% (n=220)	3.3% (n=46)	2.9% (n=41)	21.8% (n=307)	52% (n=734)	2.1% (n=30)	24.1% (n=340)

Note. Test results for patients referred for a repeat test come from the first Cytosponge test. Results based on the unweighted Cytosponge cohort.

Source: Impact Evaluation data

Some variations in patients' diagnostic pathways occurred, however these had only a small effect on the overall impact of Cytosponge on reducing endoscopy demand.

Some patients (7.5%, (n=79)) who received a negative Cytosponge result were also referred for an onward endoscopy, and a small number of patients who received a positive Cytosponge result did not have an onward endoscopy recorded for them in the dataset (n=18 of 129, inclusive of 8 patients who were discharged, 5 patients referred for a repeat test, and 5 patients with an unknown subsequent action). Hence, the recommended diagnostic pathway following a Cytosponge test was not followed for these patients. Possible reasons for this are discussed below and should be further investigated in preparation for a national roll-out of Cytosponge.

Firstly, a Cytosponge test can test for multiple different pathological indications, in addition to the BO pathology (including but not limited to acute inflammation, the presence of Neutrophils in the columnar, Candida and Ulcer Slough). In cases where patients received a negative Cytosponge test for atypia and other biomarkers and were referred for an onward endoscopy, clinicians might still have deemed the pathological report findings appropriate for an endoscopy referral. Clinical judgment should be the primary factor for determining the patient pathway.

Secondly, variations to the recommended patient diagnostic pathway could also be explained by a lack of confidence in the accuracy of the test amongst clinicians. Qualitative data from interviews with clinicians suggested that a lack of clinician/nurse confidence in the Cytosponge test results may have influenced whether patients were discharged or referred onwards for an endoscopy. This indicated that while Cytosponge helped reduce demand for an endoscopy, the reduction in demand could have been greater if clinician confidence in the test results was improved.

A lack of confidence in the Cytosponge test was a theme that arose in three sites that participated in deep dive interviews. In some instances, clinicians reported not fully understanding/appreciating “the science” behind the device and therefore instead of “putting patients through another Cytosponge test”, they referred them straight for an endoscopy. Clinicians also reported the re-referral of patients by GPs for endoscopy despite receiving negative/normal Cytosponge results. However, clinicians’ confidence in the accuracy of the Cytosponge test results may have increased over the course of the pilot, as indicated by preliminary evidence from the Impact Evaluation analysis showing a reduction in the number of patients undergoing an endoscopy following a Cytosponge test over time (discussed below). Of note, the COVID-19 pandemic might have also affected clinicians’ confidence in the Cytosponge test and led to concerns about missing pathology results.

Furthermore, GPs were not always aware their patients may have received a Cytosponge test instead of endoscopy at the point of referral. Although GPs were sent Cytosponge test results, it was reported that this information was not always read or fully understood. It should be noted that a decision was made that GPs should not be made aware of the Cytosponge pathway as part of the pilot, as this had the potential to influence the diagnostic pathway of patients. Hence, it will be important to provide adequate training to GPs and primary care teams as part of a national implementation of the Cytosponge pathway.

Alternatively, the observed discrepancies between the results of the Cytosponge test and the subsequent actions of patients could be explained by data entry errors at the sites, in particular for patients who received a positive test result and no apparent onward endoscopy. Where possible, discrepancies were investigated by comparing data entered across multiple data items to confirm the patient pathway. The small number of discrepancies remaining are due to the limited number of data items reported and some missing information for data reported by the sites. These discrepancies could be explored with further investigation, particularly for those cases where patients with positive results were discharged following a Cytosponge test.

Additional analysis of the Impact Evaluation data to estimate the reduction in endoscopy demand if all patients adhered to the “ideal” pathway (i.e., assuming that patients with a negative Cytosponge test did not have an endoscopy and those with a positive or uncertain Cytosponge test did) indicated an absolute reduction of 79% in endoscopy demand. This suggests that if all patients had followed the recommended pathway, the impact of Cytosponge on endoscopy demand would have been nearly the same (compared to 80.7% avoiding endoscopy in the main Impact Evaluation findings) or a further small reduction in demand (compared to approximately 73% avoiding endoscopy when accounting for missing data, as described above). The variation in diagnostic pathway is therefore likely to have only a small impact on the effectiveness of Cytosponge in reducing endoscopy demand. This means that clinicians should not be encouraged to strictly adhere to the recommended pathway if they have clinical concerns that are not aligned to the pathology results.

The effectiveness of Cytosponge in reducing endoscopy demand increased during the pilot period.

The proportion of Cytosponge patients undergoing an endoscopy decreased over time.

Impact Evaluation data showed that the number of Cytosponge patients who underwent an endoscopy following a Cytosponge test decreased over time, according to the date of their triage for Cytosponge. Specifically, the proportion of patients who had an endoscopy decreased from 27.9% for patients with an early triage date (i.e., before or in July 2021) to 8.1% for those with a late triage date (i.e., in or after January 2022). This indicates an absolute reduction of 20% in endoscopy demand amongst Cytosponge patients over time.

This variation in the pattern of endoscopy rates over time may be explained by increased clinician confidence in the accuracy of Cytosponge. Alternatively, this trend could be explained by differences in the risk profile of patients in the early versus late triage time period for Cytosponge (e.g., patients with an early triage date might have had more severe symptoms than those with a late triage date, which made them more likely to require an endoscopy). This trend may be partially explained by the fact that for a small number of Cytosponge patients who had a subsequent action of endoscopy, the endoscopy outcome might have not been observed within the pilot period because they had a late triage date (i.e., in or after January 2022) and their endoscopy occurred after the end of the data collection period (n=38 patients affected). However, this is only likely to account for some, but not all of the observed decline over time.

The proportion of Cytosponge patients who underwent an endoscopy also varied across sites. For example, at one site (n=58) there were no patients who underwent an endoscopy. At two sites, only approximately 5% of patients underwent endoscopy (n=169 and n=41). By comparison, in two sites, around half of the patients eligible for Cytosponge (n=58 and n=36) underwent an endoscopy within the time period of the Impact Evaluation analysis.

The proportion of patients who underwent an endoscopy at each site was descriptively unrelated to the time the site started submitting data for the Cytosponge pilot, hence these site-level differences can be attributed to other site-specific factors (for example, capacity of sites to carry out endoscopies).

Cytosponge re-testing is unlikely to have a substantial impact on endoscopy demand

Cytosponge re-testing is unlikely to have a substantial impact on endoscopy demand, given the small proportion of patients recommended for a repeat Cytosponge test and the small proportion of onward endoscopy referrals after the second test.

The Impact Evaluation data identified 30 patients (2.1%, n=1,411) who were referred for a Cytosponge retest. Of these, 23 (76.7%) patients successfully completed a second Cytosponge test, of which just under half (43.5%, n=10 of 23) were subsequently discharged or monitored. No patients were further re-tested, but 21.7% (n=5 of 23) were referred to have an endoscopy (routine or unknown urgency) and none of these patients were found to have BO.

The impact of Cytosponge on overall endoscopy waiting times, which were declining across NHS sites in England over the evaluation period, is unclear.

The proportion of patients at Cytosponge pilot sites waiting more than six weeks for an endoscopy (including colonoscopy, cystoscopy, flexi sigmoidoscopy and gastroscopy) declined from 51% to 45% between March 2021 and March 2022 (NHS England, 2022b). However, this trend was also seen across all NHS sites in England, with the total proportion of patients waiting over 6-weeks to receive an endoscopy dropping from 46% in March 2021 to 35% in March 2022. This suggests that the reductions in patients waiting more than six weeks at Cytosponge pilot sites may not have occurred solely because of the implementation of Cytosponge. At the same time, data from sites that submitted counterfactual data also show that patients might have received endoscopies more quickly due to Cytosponge effectively removing patients from the waiting list (see Evaluation Question 2). Further analysis is therefore required to quantify the impact of Cytosponge on waiting times for endoscopy.

Evaluation Question 2: Patient outcomes

What impact does Cytosponge have on patient outcomes?

Patient outcomes in the context of this Cytosponge pilot evaluation refers to: (1) Diagnostic outcomes (i.e., diagnosis of BO) of patients who underwent a Cytosponge test; (2) Diagnostic waiting times to various points along the patient diagnostic pathway (i.e., triage or diagnosis); and (3) Acceptability and safety of the Cytosponge test. It does not refer to longer term health outcomes in relation to BO or OC, due to the relatively short follow-up time period for this evaluation and the burden of data collection for sites if multiple diagnoses were considered as a priority.

Analysis of the impact of Cytosponge on patient outcomes focuses on these three key areas, with results drawn primarily from data collected and analysed within the Impact Evaluation analysis of Cytosponge and counterfactual patients. All descriptive analyses, and those only involving Cytosponge patients, were conducted on the full unweighted cohorts. Comparative analyses were conducted on the weighted cohorts of Cytosponge and counterfactual patients.

Diagnostic outcomes for patients who underwent a Cytosponge test

Cytosponge patients were appropriately prioritised through the pathway based on their test result and urgency for endoscopy.

The subsequent actions and outcomes for Cytosponge patients who completed the test, across all test results, and stratified by positive, uncertain, and negative test results, are summarised in Table 9.

Table 9 Subsequent actions and outcomes of patients who successfully completed a Cytosponge test, stratified by test results

	All test results N (%)	Positive test results N (%)	Uncertain test results N (%)	Negative test results N (%)
Completed Cytosponge	1411 (100%)	129 (100%)	128 (100%)	1060 (100%)
Subsequent action				
Discharge	734 (52.02%)	8 (6.2%)	2 (1.56%)	711 (67.08%)
Urgent endoscopy	46 (3.26%)	23 (17.83%)	11 (8.59%)	10 (0.94%)
Routine endoscopy	220 (15.59%)	77 (59.69%)	64 (50%)	62 (5.85%)
Unknown urgency endoscopy	41 (2.91%)	11 (8.53%)	12 (9.38%)	7 (0.66%)
Re-test	30 (2.13%)	5 (3.88%)	20 (15.62%)	4 (0.38%)
Other	176 (12.47%)	2 (1.55%)	13 (10.16%)	147 (13.87%)
Missing	164 (11.62%)	3 (2.33%)	6 (4.69%)	119 (11.23%)
Completed endoscopy (% out of those who were referred for an onward endoscopy)	223 (73%)	81 (72.97%)	57 (65.52%)	64 (81.01%)
BO	25 (11.21%)	22 (27.16%)	2 (3.51%)	0 (0%)
OC	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Inflammation	19 (8.52%)	7 (8.64%)	3 (5.26%)	9 (14.06%)
Intestinal metaplasia	8 (3.95%)	7 (8.64%)	1 (1.75%)	0 (0%)
Ulcer	3 (1.35%)	1 (1.23%)	1 (1.75%)	1 (1.56%)
Oesophagitis	12 (5.38%)	6 (7.41%)	4 (7.02%)	2 (3.13%)
Hiatus Hernia	29 (13%)	10 (12.35%)	8 (14.04%)	11 (17.19%)
Other	10 (4.48%)	0 (0%)	5 (8.77%)	2 (3.13%)

Note: Results based on the unweighted Cytosponge cohort. Note that the "All test results" column includes patients with missing/ unknown test results which are not shown separately. Percentages are given by column.

Source: Impact Evaluation data

Cytosponge patients with positive test results were more likely to be referred urgently for an endoscopy compared to those with uncertain or negative results, and these patients had the highest prevalence of Barrett's Oesophagus.

Of the Cytosponge patients with a positive test result, 86% were referred for a subsequent endoscopy (n =111 of 129; 17.8% urgently, 60% routinely and 8.5% referred with unknown urgency). This compares to 68% of those with uncertain test results (n=87 of 128) and 7.5% of patients with negative results (n= 79 of 1060). Furthermore, the ratio of urgent to routine referrals was highest for those with positive results, with approximately 1 in 4 referrals being urgent (n=23 of 100), compared to approximately 1 in every 7 referrals for those with uncertain results (n= 11 of 75) or negative results (n=10 of 72). This indicates that high risk patients were appropriately triaged through the diagnostic pathway, both in terms of receipt of an onward referral for endoscopy and the urgency of the referral.

Although it was not possible to determine the specific subsequent actions for all patients (either due to missing data or a lack of detail), it is most likely that these patients were discharged given the absence of further information on endoscopy or outcomes. This hypothesis is consistent with the fact that the highest proportions of “Other” or “Missing” subsequent actions were observed for those with negative test results, and these patients would be most likely to be discharged according to guidelines. For a small number of patients, the subsequent actions observed appeared contradictory to clinical guidelines (e.g., discharge following a positive test result), but it was not possible to determine whether these instances occurred due to data entry errors or true deviation from guidelines because of a lack of further information on these patients.

Cytosponge patients with positive results who were referred for and completed their endoscopy had the highest prevalence of BO at 27.2% (n=22 of 81). This compares to only 3.5% of patients with uncertain results (n=2 of 57) and zero patients with negative results (n=0 of 64) completing endoscopy. Even if all the uncertain results were in fact negative, those who tested positive would still be 15.6 [relative risk, 95% CI: 3.8 to 64.6] times more likely to have BO than those who tested negative but went on to have an endoscopy. Although clinical outcomes could only be assessed for those undergoing endoscopy, these findings further indicate that patients at high risk were effectively triaged, and the risk of missed BO diagnoses is low.

Across all test results, the observed prevalence of BO was 1.8% amongst patients completing the test, rising to 11.2% in those referred for and completing an endoscopy. The estimated prevalence of BO in patients with gastro-oesophageal reflux symptoms varies significantly across the literature. A UK based trial of Cytosponge in primary care found rates of BO of 1-2% in both the Cytosponge and usual care groups, where not all patients underwent diagnostic endoscopy (Fitzgerald et al., 2020). This is broadly comparable to the overall estimate observed for patients completing a Cytosponge test in this evaluation. Other estimates from systematic reviews range from 3% to 9% in different patient groups across western countries (Leonardo Henry Eusebi et al., 2021; Marques de Sá et al., 2020; Qumseya et al., 2019), although these may not be directly comparable due to differences in patient selection and outcome ascertainment.

The increase in the proportion of patients diagnosed with BO from 1.8% in those completing the test to 11.2% in those undergoing endoscopy, indicates that Cytosponge can triage patients accurately and is unlikely to miss diagnoses compared to endoscopy alone (see below for counterfactual comparison). Other endoscopy outcomes reported by sites included inflammation (8.5%), intestinal metaplasia (3.6%), ulcer (1.4%), oesophagitis (5.4%), and hiatus hernia (13.0%), although note that sites were instructed to report the most severe outcome observed of these non-BO outcomes, so the prevalence of less severe outcomes may be underestimated.

Rates of BO diagnosis were similar in the Cytosponge and counterfactual groups.

The proportion of patients in the weighted Cytosponge group with a diagnosis of BO following endoscopy was higher than in the weighted counterfactual group (i.e., 2.0% vs 1.4%), representing a relative difference of around 40%. However, it should be noted that since few patients were identified as having BO in both groups, the difference between the Cytosponge and counterfactual groups was not statistically different (p=0.64) and such formal comparisons are likely to be underpowered.

Waiting times across the Cytosponge patient diagnostic pathway

It is worth noting that the Impact Evaluation analysis may show longer timeframes than would be seen in the 'steady state' phase of the pilot, or a future roll-out. This is because during the start-up phase of the pilot, clinicians were advised to prioritise the referral and triage of patients who had been on the waiting list for the longest time, thus waiting times may be greater for patients who were triaged during the earlier phase. Furthermore, this was the first time that the Cytosponge test was implemented at the sites, which might have increased the time taken to triage patients, administer the test, and provide test results. A national roll-out with appropriately resourced robust referral pathways and processes would likely see reduced timeframes overall.

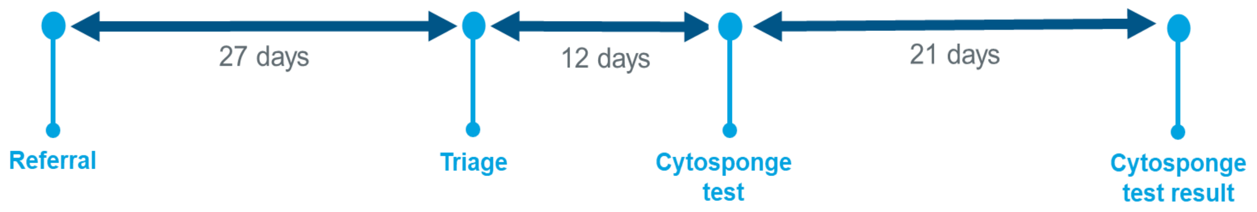
On average, the total time from referral to Cytosponge test result was 60 days for all patients.

The time from referral to Cytosponge test result can be broken down by four key timepoints: referral, triage, Cytosponge test, Cytosponge test result. The results in this section explore the time taken between each of these timepoints (as illustrated in Figure 6).

First, the median time from referral to triage for Cytosponge was 27 days. Waiting times from referral to triage were expected to be relatively long due to sites prioritising patients who had been on the waiting list for endoscopy the longest. In a future roll-out, the time from referral to triage may be shorter if patients have direct access to a Cytosponge test.

Median waiting times from triage to Cytosponge test were, however, relatively short at 12 days, and 50% of patients received their first Cytosponge test within approximately six weeks from their original secondary care endoscopy referral (i.e., 39 days).

Figure 6. Average (median) time from endoscopy referral to Cytosponge test result



Note: Results based on the unweighted Cytosponge cohort. Source: Impact Evaluation data

Following the Cytosponge test, patients waited on average 21 days to receive their test results. The three-week waiting time to receive a Cytosponge test result may lengthen the overall time that a patient remains in the pathway. This is expected and, according to the Cytosponge clinical guidance, patients are advised that test results will be available in approximately 2-3 weeks following the Cytosponge test. Thus, strategies to reduce the time taken for patients to receive a Cytosponge test result should be considered for a national roll-out of the Cytosponge test. These may include, for instance, processing the pathology test results more quickly and ensuring sites have sufficient staff capacity to read the results and communicate them to the patients. Cyted data showed that the turnaround time for the pathology results was around 11 days, on average, so it may be particularly important to focus on decreasing the time it takes for sites to communicate results to patients.

In most cases, Cytosponge patients waited longer than counterfactual patients to be discharged, with length of time waiting dependent on Cytosponge test result and subsequent endoscopy referral type.

As discussed in the limitations of the Impact Evaluation methodology (see Section 2), the following comparative results should be considered in the context of their limitations. More specifically, eligibility for counterfactual patients was determined by individual sites, and there may be some variations in the approach used by sites to ascertain the eligibility criteria. Furthermore, Cytosponge patients were primarily those who accepted the test, and the exact timing of exit from the diagnostic pathway could not be determined for some Cytosponge patients (around 15%). These factors have the potential to introduce bias in these results, with plausible explanations for possible bias in either direction. Supporting sensitivity analyses, exploring these possible biases are summarised in supporting documents, separate to this report.

Patients who received a Cytosponge test waited similar times to receive a BO diagnosis compared to counterfactual patients.

Despite overall longer waiting times for Cytosponge patients, for patients with a BO diagnosis the waiting times to receive a BO diagnosis were similar between Cytosponge and counterfactual patients. There was no evidence of a difference in the time taken to receive a BO diagnosis during follow-up ($p=0.69$). However, the number of patients who received a BO diagnosis was small in both groups, so this result should be interpreted with caution. This result may be explained by both appropriate triaging of Cytosponge patients at high risk of BO, coupled with the shorter time to endoscopy for those referred urgently as described above. In other words, despite potential delays in the diagnostic pathway for Cytosponge patients in general (e.g., due to the time between the Cytosponge test and result being made available), the patients at highest risk were appropriately triaged for urgent endoscopy, and those with a BO diagnosis moved through the pathway quickly enough to overcome any initial delays.

All other Cytosponge patients (except those who received a BO diagnosis), were more likely to wait longer than counterfactual patients to be discharged or receive their endoscopy result.

Patients were followed until the end of their diagnostic pathway, defined as the latest of their date of endoscopy or date of a negative Cytosponge test result. Hence, for Cytosponge patients with a negative test result who were not referred for a subsequent endoscopy, the end of their diagnostic pathway was the date of their negative test result. For all other patients (counterfactual patients and Cytosponge patients with a positive, uncertain or unknown test result, and Cytosponge patients with a negative test result who were referred for a subsequent endoscopy), the end of their diagnostic pathway was their date of endoscopy.

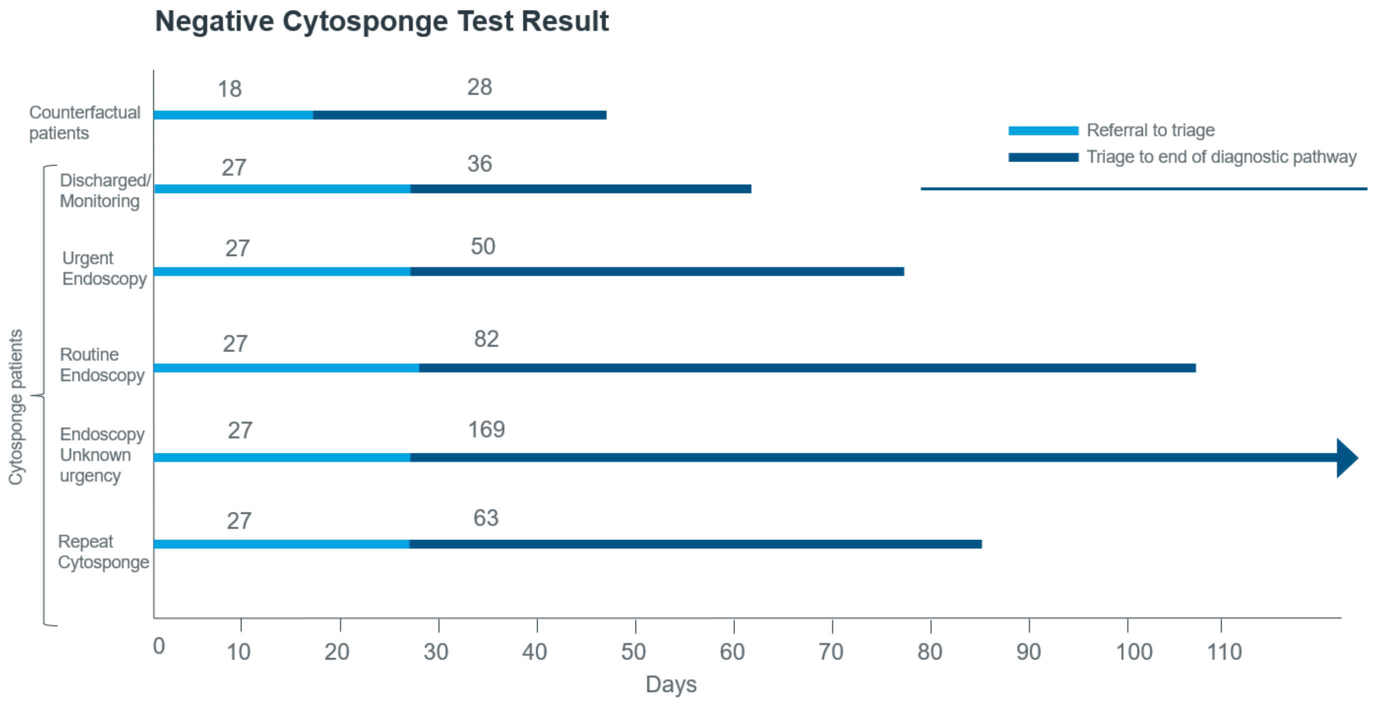
Amongst patients who completed a Cytosponge test, waiting times from referral to the end of the diagnostic pathway were longer for Cytosponge patients compared to the counterfactual group in the weighted analysis. Specifically, Cytosponge patients waited on average 75 days from referral to the end of the diagnostic pathway (endoscopy or negative test result), consisting of 27 days from referral to triage plus 48 days [95% CI: 45 to 49] from triage to the end of the pathway, on average. Comparatively, for counterfactual patients the time from referral to the end of the diagnostic pathway (i.e., endoscopy date) was 46 days on average. The difference between the two groups in median time to the end of the pathway from triage date was statistically significant ($p<0.001$). As discussed above, since patients who were on the waiting list longest were prioritised for Cytosponge, the time between referral and triage may be artificially elongated for the Cytosponge patients in this pilot, although differences between the groups in this respect were partly accounted for in the weighted analysis.

The differences observed between the two groups can be further understood by considering the time from triage to the end of the diagnostic pathway, depending on their Cytosponge test result and subsequent action (discussed below).

Cytosponge patients with a negative test result who were discharged waited longer to exit the diagnostic pathway on average compared to counterfactual patients. However, Cytosponge patients were less likely to experience very long waiting times (60+ days) compared to counterfactual patients.

Patients with a negative Cytosponge test result who were subsequently discharged waited on average 63 days from referral to the end of their diagnostic pathway (i.e., date of a negative Cytosponge test result). This was based on waiting times of 27 days (median) from referral to triage followed by 36 days [95% CI: 35 to 36] (median) from triage to test result. Note that the waiting time from triage differs slightly from the 33 days from triage to test result presented above since the 33-day figure covers all Cytosponge patients in an unweighted analysis. However, the similarity in these values indicates that the elongated waiting time for these patients compared to counterfactual patients may be primarily driven by the time taken to receive the Cytosponge test result. In contrast, results from endoscopy may be made available to patients on the same day of the examination, or within two weeks from the date of the endoscopy if a biopsy is also performed as part of the examination.

Figure 7. Median time (days) to the end of the diagnostic pathway in counterfactual patients vs Cytosponge patients with negative test results, stratified by their subsequent actions.



Note: Results based on the weighted comparative analysis of time to end of the diagnostic pathway from triage date. Proxy triage dates were used for the counterfactual group in order to ensure temporal alignment in the follow-up of counterfactual and Cytosponge patients.

Source: Impact Evaluation data

Although *median* waiting times from triage were longer for Cytosponge patients than counterfactual patients, the proportion of patients waiting longer than 60 (12%) or 90 (4%) days was lower for Cytosponge patients who tested negative and were then discharged, compared to counterfactual patients (24% and 18%, respectively) (See Table 10). This indicates that although most Cytosponge patients waited longer to reach the end of their diagnostic pathway, patients who had a negative result and were subsequently discharged were more likely to avoid the very long waiting times observed for some patients undergoing endoscopy alone.

Table 10 Proportion of patients waiting to reach the end of their diagnostic pathway at different time points during the follow-up from triage in the weighted Cytosponge (testing negative and then discharged) and counterfactual groups.

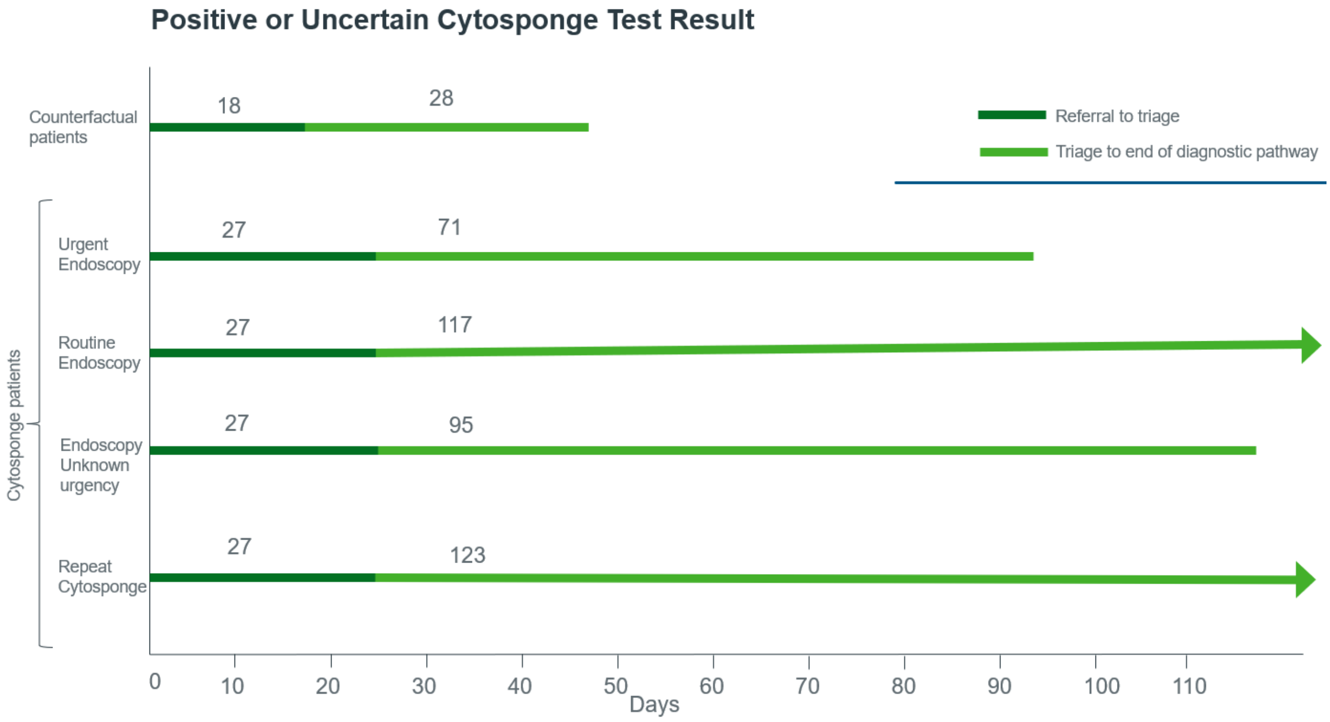
Time point	Cytosponge patients (testing negative and then discharged, weighted)	Counterfactual patients (weighted)
15 days	95% (94 – 97%)	73% (67 – 80%)
30 days	61% (58 – 65%)	46% (39 – 54%)
60 days	12% (10 – 15%)	24% (18 – 31%)
90 days	4% (3 – 6%)	18% (13 – 24%)

Source: Impact Evaluation data

Cytosponge patients with a routine onward referral waited longer than patients with an urgent onward endoscopy referral.

Across all test results (positive, uncertain, and negative), Cytosponge patients referred for an urgent endoscopy following the Cytosponge test received an endoscopy faster than those referred for a routine endoscopy. For instance, in patients with positive or uncertain test results who were referred for an endoscopy, the median time from triage to the end of their diagnostic pathway (i.e., endoscopy) was 71 days for those referred for an urgent endoscopy [95% CI: 54 to 116] and 117 days for those referred for a routine endoscopy [95% CI: 103 to 141] (see Figure 8). A similar pattern of results was observed in patients with negative test results who were nonetheless referred for an endoscopy.

Figure 8. Median time (days) to the end of the diagnostic pathway in counterfactual patients vs Cytosponge patients with positive or uncertain test results, stratified by their subsequent actions.



Note: Results based on the weighted comparative analysis of time end of diagnostic pathway from triage date. Proxy triage dates were used for the counterfactual group in order to ensure temporal alignment in the follow-up of counterfactual and Cytosponge patients.

Source: Impact Evaluation data

Waiting times for Cytosponge patients decreased the longer Cytosponge was in place.

The number of patients with long diagnostic waiting times decreased during the pilot amongst Cytosponge patients.

The time taken for Cytosponge patients to reach the end of the diagnostic pathway decreased over time. Specifically, the median time from triage to the end of the diagnostic pathway for Cytosponge patients decreased from 55 days [95% CI: 52 to 67] in the early time period for Cytosponge triage (i.e., before or on 31/07/2021) to 43 days [95% CI: 37 to 46] in the late time period for triage (i.e., on or after 01/01/2022). A similar pattern was seen across different time points of the follow-up period. For instance, the proportion of patients still in the diagnostic pathway at 60 days following triage was 44% [95% CI: 39% to 51%] in the early triage period compared to 34% [95%CI: 29% to 39%] in the late triage period. At 90 days post triage, the proportion of patients still in the diagnostic pathway further reduced from 33% [95% CI: 27% to 39%] in the early period to 27% [95% CI: 23% to 32%] in the late period.

By contrast, there was little change in the median waiting times to endoscopy within counterfactual patients from the early (23 days [95% CI: 20 to 34]) to the late (22 days [95% CI: 16 to 37]) triage period. However, the number of patients with long waiting times also decreased over time for counterfactual patients. For instance, at 60 days post triage, the proportion of patients who had not yet received an endoscopy was 24% [95% CI: 18% to 32%] in the early period compared to 5% [95% CI: 1% to 36%] in the late triage period.

Data from both Cytosponge and counterfactual patients show a reduction in the number of patients with long diagnostic waiting times over the course of the Cytosponge pilot. This may indicate increased efficiency of endoscopy services because of reduced endoscopy demand amongst the sites involved in the pilot. It may also be explained by increasing clinician confidence in the Cytosponge test over time, resulting in more patients with a negative test result being discharged, and the shorter waiting times for these patients (compared to those who remain in the diagnostic pathway) having greater overall impact. However, this decrease in waiting times over time could also be partly explained by a reduction in the backlogs caused by the COVID-19 pandemic amongst the sites included in the Impact Evaluation analysis.

Acceptability and safety of the Cytosponge test

Cytosponge is an acceptable and safe procedure in secondary care settings.

MI data shows that approximately 93% of patients accepted the offer to complete a Cytosponge test, indicating that Cytosponge has high acceptance rates amongst patients. This result aligns with the high levels of satisfaction observed amongst most patients who completed the Patient Experience workstream survey.

Evidence also indicates that Cytosponge is a patient-friendly and safe procedure to triage patients with reflux symptoms. 94.8% (n=1,411 of 1,489) of patients who attended the visit successfully completed the Cytosponge test, with the majority of patients (86.9%, n=1,294 of 1,489) needing only one attempt to swallow the sponge. Furthermore, no serious adverse events were reported by sites during the evaluation period.

Overall, these results provide supporting evidence of the acceptability and safety of Cytosponge as a triaging tool for patients with low-risk reflux symptoms in secondary care settings.

Evaluation Question 3: Patient experience

What impact does Cytosponge have on the diagnostic experience of patients?

The below discussion on patient experience is articulated in four parts: (1) Overall satisfaction, (2) Before the test, (3) During the test, and (4) After the test. The discussion is primarily based on analysis completed by the Patient Experience workstream, with supportive evidence from the Impact Evaluation workstream and analysis of the MI data.

Overall patient satisfaction

Most patients (82%) were satisfied with their experience of the Cytosponge test.

> *“...it just went very smoothly, and the discomfort subsided quite quickly. So, I would definitely recommend [Cytosponge to others]”*

> “*If you're talking cancer, the sooner you get interventions and get treatment, the more likely the positive outcome is going to be, so if that's the case…getting things found out as quickly as possible is important, so Cytosponge enabled me to do that. For me, that was a win-win situation.*”

In the Patient Experience survey, 82% of patients (n=267) agreed or strongly agreed they were satisfied with their experience of the Cytosponge test. These results are broadly consistent with previous studies showing that up to 97% of patients reported a positive experience of the Cytosponge test across primary and secondary care sectors (Freeman et al., 2017; Ghimire et al., 2023; Heberle et al., 2017; Januszewicz et al., 2019; Kadri et al., 2010)

Perceptions of respect and dignity during the testing process were overwhelmingly positive. 97% of respondents to the patient experience survey reported that their respect and dignity was maintained at all times during their Cytosponge diagnostic test. This compares favourably to the National Cancer Patient Experience Survey 2021 which had a comparable score of 89% (NHS England, 2022a).

Patients interviewed often stated that they would not only book the test again for themselves, but also would recommend the test to a friend or family member, or already have, further indicating their satisfaction with the process.

A number of reasons for their positive levels of satisfaction were explained by patients. These included:

- Cytosponge was less invasive than an endoscopy. This was explained both by those who had and those who had not had an endoscopy prior to the Cytosponge test or after, so could be based both on experience and on perception.
- Patients were reassured by Cytosponge results because the Cytosponge test "*scrapes cells rather than assessing visually"*.
- Fewer staff were needed and "*it does not need to be performed in a theatre*".
- Timeliness and speed of attaining their appointment and receiving an answer and peace of mind, and the duration of the procedure itself.

> *"I think the fact that I knew that cells were being taken and looked at, I felt quite happy that I'd gone that route."*

While patient satisfaction levels were high overall, some small variations occurred by test result and patient age.

Patient satisfaction differed by result type (i.e., positive, requiring further testing; or negative, resulting in a discharge). For instance, higher satisfaction levels were reported more frequently among patients who were not referred for an onward endoscopy (88%, n=184 of 209) compared to patients who were referred for onward endoscopy (76%, n=66 of 87).

> *"I might not have had to have the endoscopy and because I had it, I think I then got the endoscopy quicker than I might have done otherwise, so all good. I had had breast cancer in the past so when someone tells me there are abnormal cells … had a real worry, so I was really glad to get the sponge and then the fast endoscopy."*

There was very little difference in patients reporting to be happy with their decision to take the Cytosponge test rather than staying on the endoscopy waitlist between those who were referred for an endoscopy (82%, n=73 of 89) and those who were not referred (84%, n=177 of 209). However, patients who reported their original issue was not resolved were least likely to be happy to have received the Cytosponge test over waiting for an endoscopy (66%, n=71 of 108) compared to those who reported that their issue was resolved at least to some extent (91%, n=201 of 220).

Generally speaking, patients from older age groups reported to be more satisfied with Cytosponge than those from younger age groups, but the differences are small. Those in the oldest age group (75-84) were most satisfied with 63% (n=12) reporting complete satisfaction. This compares to 45% (n=13) in the youngest age group (25-34). Older patients were also more likely to report that their original issue had been resolved as far as possible (95%, n=18 for those aged 75-84 compared with 48%, n=14 for those aged 25-34). This is to be expected given the underlying cause of reflux symptoms in younger people is less likely to be caused by atypia or TFF3 and therefore less likely to be detected by the Cytosponge test. Therefore younger patients are more likely to require an onward endoscopy and thus lengthening their time to receive a diagnosis. It is also important to point out that there is existing evidence which shows older patients are generally more likely to report a positive experience than younger patients (NHS England, 2022a)

Patients preferred Cytosponge over endoscopy.

Despite reported satisfaction with Cytosponge being similar for both patients who have (80% (n=92)) and haven't (83% (n=173)) received an endoscopy before, patients with a previous endoscopy experience explained that the Cytosponge test was a preferable alternative to an endoscopy. Their descriptions of endoscopy included it being painful, traumatic, violating, invasive, and time-consuming (i.e., time spent at the hospital and recovering).

> *"As they withdrew the sponge, there could be some slight unpleasantness and there could be some minor sort of effects afterwards, but actually is less invasive and less unpleasant than having an endoscopy."*

Positive satisfaction responses were not affected by any reported discomfort during the Cytosponge test.

> *"Yes [it was] uncomfortable but [it had] low impact. You can drive afterwards [and it] doesn't stop you from doing things."*

A small proportion of patients were not satisfied with the Cytosponge test, but at the same time were still happy to have taken it.

Reasons patients interviewed gave for not being satisfied included:

- Problems with completing the test. These included being unable to complete the test due to an issue with their gag reflex and not being able to keep the sponge down.
- Poor understanding of what the test results show and mean. For example, one patient was not satisfied due to their lack of clarity regarding what the test results could show, lack of awareness of being removed from the endoscopy waiting list, and discontent with their HCP recommending medication after the test to address their persisting issues. This patient reported feeling "mis-sold," and stated:

> *"At no point was I told that it was just to look for a sort of cancer cell and stuff. And it's actually very painful, very, very briefly, as it comes out of the back of your throat."*

However, these patients were still happy with their decision to undertake a Cytosponge test due to having peace of mind in receiving a result quicker than waiting for an endoscopy.

> *"Let's put it this way. I was very happy there was an alternative. Otherwise, I'd have been waiting for an endoscopy for God knows how long."*

Findings from the 1:1 patient interview validated the survey results. Patients who did not feel satisfied with the Cytosponge test reported either a lack of awareness that the Cytosponge was specific to testing for only cancerous cells, or that they felt the Cytosponge did not go "deep enough" into their stomachs to collect an adequate sample. The latter, highlights how informing patients and expectation management has downstream impact on patient satisfaction post procedure.

Patient experiences before the test

Clear explanations by professionals enabled patients to make informed decisions about accepting the offer of the Cytosponge test.

Almost all patients reported that they understood, at least to some extent, the explanations given to them regarding Cytosponge and what would happen during the test (99%, n=339), and the purpose of the test (94%, n=322). Almost all patients were given a Cytosponge leaflet (92%, n=313) and almost all patients surveyed found it useful (92%, n=285). This is equitable to the National Cancer Patient Experience Survey 2021 results in which 92.6% of patients agreed they had all the information they needed in advance (NHS England, 2022a).

> *"The nurses were so nice... they explained clearly what was going to happen during the test so there were no surprises. Nothing really prepares you for the string being yanked back up, however."*

During interviews, nearly all patients explained that their choice was informed by the leaflet and the invitation to take the test from a letter and/or a phone discussion with a nurse prior to their appointment. Most patients surveyed strongly agreed (55%, n=189) or agreed (39%, n=132) that enough information was given to make an informed decision about accepting the offer of a Cytosponge test. MI data shows that across the sites, approximately 93% of patients accepted the offer of a Cytosponge test.

40% of patients reported not being informed about being removed from the upper endoscopy or gastroscopy waitlists, with some differences by site.

Overall, 40% (n=136) of patients reported that they were not informed about their removal from the upper endoscopy or gastroscopy waitlists if they were to have a Cytosponge test. An almost equal proportion – 38% (n=132) – self-reported they were told about their removal from the waitlist and the remaining 22% (n=75) could not remember.

Within this, there were site level differences regarding the information patients reported to have received. Among sites, patients recalling they were informed of removal varied from 10% to 63%. However, the numbers of patients in these categories are low. Interviews with patients showed that most were aware they would be taken off the waiting list for an endoscopy upon receiving negative results. However, satisfaction levels did not tend to differ between those who did not recall they would be removed from the waiting list and patients who did.

Patient experiences during the test

Most patients experienced no pain or just mild pain during or immediately after the test.

No serious adverse events during or immediately after testing were reported to NHSE during the evaluation period. Overall, 94% (n=277) of patients also reported experiencing only mild pain or no pain at all. Time since test did not appear to have a major influence on whether patients reported to experience pain or not. Overall, only 6% (n=17) of patients reported experiencing severe or very severe pain during or immediately after their test.

More patients reported experiencing some level of discomfort rather than pain.

Overall, 67% of patients reported experiencing mild discomfort during or immediately after the test (n=210 of 315), and just over a fifth of patients (22%, n=70) experienced severe discomfort. However, self-reported discomfort was broadly in line with the potential risks outlined in the patient leaflet (e.g., bleeding; a sore throat for up to 48 hours). Most patients (97%, n=274) did not experience bleeding, while 64% reported experiencing mild throat irritation (n=195; 25% not at all, n=76). Only 12% (n=36) experienced severe or very severe irritation. Only 12% of patients reported experiencing any other side effects (of which 4%, n=5 mild; 5%, n=7 severe; 3%, n=4 very severe; total n=212) in the survey. Some patients interviewed specified their discomfort as difficulty with the string being inserted and/or removed.

> *“I found it quite difficult to swallow the capsule because I didn't appreciate how I might react to the additional bit of the string. So, I was very well prepared for it by the Cytosponge Nurse. But actually, in practice, I didn't imagine that I would find it so difficult. Maybe I got a bit tense and maybe my throat was a bit closed compared to how I would normally be.”*

> *“The feeling of the string going down [my] throat caused very unpleasant and uncontrollable reflux reaction, a feeling of nausea, and then [when] the Cytosponge was removed I experienced discomfort and a scratch inside of my throat for the first time; but the reflux was controllable [the] second time as I was aware of that reaction and the test was completed successfully.”*

Some patients explained soreness in the chest, difficulties swallowing, burning sensations, stomach pain, retching, dry feeling in the throat, vomiting, and strong gag reactions. Such discomforts occurred both during the test and in the days following. However, most patients interviewed stated that any side effects experienced had no significant impact on their daily activities or wellbeing.

Most patients did not report experiencing any discomfort in the days following the test (94%, n=104). Those in the oldest age group were most likely to report experiencing no pain (79%, n=11).

Most patients were unconcerned with the level of discomfort they experienced.

During interviews, most patients reported that whilst they experienced some level of discomfort, it was manageable in intensity and duration, notably when compared to any experience with an endoscopy.

> *“I swallowed it without any real difficulty. It was strange rather than particularly uncomfortable, and certainly not painful. It was strangest when it was pulled back up, and that did seem to sort of scrape a bit, but again, not seriously painful.”*

Such discomfort reported during the Cytosponge test occurred when patients were swallowing the device and/or when it was removed. Patients explained the reasons for discomfort included the size of the sponge, difficulty swallowing the string, the sensation of the string in the back of the throat whilst waiting for the sponge to expand, and the nature of the device physically touching the area of the throat to induce a natural gag reflux.

Despite these experiences of discomfort, impact evaluation data showed that 87% (n=1,294) of patients were able to swallow the sponge on the first attempt. Only 9% (n=133) of patients took two attempts and 0.7% (n=10) swallowed in 3 attempts. These results show that despite some potential discomfort, most patients can easily complete the test within a single swallow attempt, indicating the ease of administration of Cytosponge.

Most patients who reported discomfort during the removal of the device noted that negative sensations were brief.

> *“It wouldn’t even come up with the wrenching, so it did get stuck. Not for long. You know, we're talking seconds.”*
>
> *“It was pain free as she takes it out very quickly, and just as it comes over the back of your throat, that was eye watering, but brief.”*

A small number of patients described their discomfort as a result of the physical size and texture of the sponge scraping the throat, and/or that it was removed too quickly or too slowly.

Cytosponge nurses played a key role in patients’ comfort levels.

Most patients interviewed praised the quality of their Cytosponge nurse on the day of their test regarding the explanations and care they received. Nursing staff were essential factors for patients being calm, informed and cared for with empathy. Some patients stated it was necessary to remain calm to mitigate possible discomfort during the test, for example, and attributed their ability to complete the test with less discomfort to the nurse.

While some patients interviewed recalled their nurse showing them the materials prior to the actual test, most who experienced discomfort or pain described the actual testing experience as a “shock” or “surprise.” Most did not expect how difficult they would find it to swallow the string and/or that the sponge would expand into an abrasive material. However, they would take the test again due to perceived benefits over an endoscopy, and that they would know what to expect. One patient explained that they did not experience any more pain or discomfort than expected because he had seen the abrasive material and was familiar beforehand, highlighting the benefits of clear and open information being provided beforehand.

Patients who had previously received an endoscopy reported their experiences of Cytosponge test more positively.

There were differences in reported pain experienced during the Cytosponge test between patients who previously had at least one endoscopy procedure compared to patients who had not. Those who had a previous endoscopy were less likely to report experiencing pain. Overall, 72% (n=73) of those patients who had a previous endoscopy reported experiencing no pain compared to 61% (n=74) of those who had not had an endoscopy before. Older patients who were more likely to have had a previous endoscopy tended to therefore have more knowledge of how the two tests differ, and this awareness likely influenced their satisfaction levels.

Of those patients reporting that they experienced pain, patients who had not previously had an endoscopy reported experiencing mild pain (34%, n=65) at a higher rate than patients who had an endoscopy test in the past (21%, n=21). However, patients' reported experiences of severe or strongly severe pain did not notably differ between groups (8%, n=8 for patients who had an endoscopy before; 5%, n=9 for those who had not).

Patient experience after the test

Most patients were satisfied with the time they waited to receive their Cytosponge test results.

Just under a fifth of patients surveyed (19%, n=58) reported that they received their test results in under two weeks. The majority of patients (59% n=175) reported that they received their results in two to four weeks. This is in line with findings from the impact evaluation which showed the median time from Cytosponge test to receiving their results was 21 days (3 weeks). Of the remainder, 8% (n=25) reported they received their results in four to five weeks, and 14% (n=43) waited longer than 5 weeks for their results. Test result timeframes did vary by site, with patients more likely to receive results quickly in sites which had performed fewer Cytosponge tests.

Patients interviewed often did not recall exactly how long they waited for their results. However, nearly all stated they were happy with the time they waited and often described it as quick. In some cases, even those few patients who recalled waiting between two and three months for results described this as quick, perhaps indicating the low expectations that some patients have regarding timeframes for test results. A similar situation regarding patient perceptions of waiting times is seen in other studies too, for example the National Cancer Patient Experience Survey 2021 showed that 81.9% of patients felt the time they had to wait for their diagnostic test was 'about right' (NHS England, 2022).

> *"...I was told somebody would contact me with it [the results], you know, within a couple of weeks. Just with the results, which they did."*

Patients who recalled having quicker results from a past endoscopy procedure also had a positive perception of their time to wait for results, and overall preferred the Cytosponge test.

> *"I wasn't sort of sitting at home thinking, oh, another day has passed, what's going on? It was fairly quick, and I don't remember having any issues at all about that."*

> *"The fact that I can't remember [how long it took to receive the results] makes me think that I wasn't anxious about it."*

Those with longer wait times often stated they were happy with that time period as they understood the test to be taken to a laboratory and took time to process, even when compared to past endoscopy experience in which results were received the same day.

> *"The only issue was they said it would be two weeks, but obviously it must have taken longer at the lab, because it was in fact four weeks, but I wasn't concerned."*

A few interviewees recalled waiting between six and eight weeks and were still happy and perceived this as quick, particularly as it was during the COVID-19 pandemic which they understood was a challenging situation.

> *"I think it was about six weeks. I understand about the fact that, yes, we'd like our results instantly, and it'd be nice to have them in the same day. But you know, you have to realise that you are in a queue and there are other people before you… the systems take time to work, and they don't hold them up on purpose… through COVID. You just have to wait and just be thankful that we live in a country where there is that availability, you know, the services are available immediately."*

> *"Given the circumstances, I thought it was reasonable... I don't remember how long it was exactly. But given the circumstances, I was aware I wasn't waiting for months. So, it wasn't like a bad experience where I've been scratching my head for ages thinking where are these results? What's going on? It was nothing like that. The results just came so it was quicker than anticipated. So yeah, it was good, especially given all COVID was going on."*

Patients' acceptability of the wait time for their Cytosponge test result may be affected by the nature of the results. Patients did report expecting to receive results more quickly if they showed anything of concern.

> *"I presumed it would take two or three months, I would have thought, unless they found something untoward."*

Only one patient directly expressed that they were not happy with the time-period for results, as they were told they would receive the results in 1-2 weeks. After this period, they rang and received their results by phone.

Most patients who received an onwards referral for endoscopy were positive about their waiting period.

Patients interviewed who received an onwards referral for endoscopy expressed positive sentiments regarding their waiting periods. According to the Impact Evaluation data, patients who were referred for an urgent endoscopy typically received a BO diagnosis or confirmed test result approximately twice as fast as those with a routine endoscopy as a subsequent action (See Figure 8).

> *"... she [the Cytosponge nurse] said that they had identified some abnormal cells and I needed to go for an endoscopy to see if it was malignant and then they referred me straightaway and, as I say, I had the endoscopy very quickly."*

> *"… [the referral time] was reasonably quick. They [the clinician] spoke to somebody, you know, that deals with appointments or whatever, and I got an appointment quite quickly afterwards. I didn't go back to the bottom of the waiting list, I remained at the top."*

There were specific situations that a few patients experienced which affected time frames. For instance, only one patient of those interviewed required a Cytosponge re-test in which both tests failed to provide an adequate tissue sample, and thus was referred for a subsequent endoscopy. However, even in this case the patient did not express concern in relation to the amount of time they waited between tests:

> *“It's probably mitigated by the fact that, you know, I really wasn't experiencing any problems. The tests were as a check-up rather than a reaction to a problem.”*

Although very specific cases, these highlight the importance of understanding expectations for all patients, which may differ depending on individual situations and reasons for the test (e.g., to further explore the cause of current negative symptoms, or a routine check-up on a reflux medication), and managing these appropriately.

Most patients were pleased with their contact method, but this was often contingent on the nature of the results.

Most patients received their test results by mail (67%, n=203) or by phone (28%, n=84). Some patients explained in their interviews that if the result was positive, they would not wish to receive this information by post or a phone call which they were unprepared for (e.g., receiving a call from the hospital during work), but would prefer something more personal which allowed them to ask questions in an appropriate setting.

There were also differences in the level of personalisation amongst letters, with some patients receiving only a test result, and others receiving a more tailored response with a plan of action (e.g., to take a new medication) and/or an appointment to discuss actions. Approaches for communicating and delivering test results should be carefully considered in any future roll-out, potentially including how to ensure they are appropriate for different patient groups.

> *“I would have preferred a booked telephone appointment to receive my results so I could be prepared.”*

With regard to the clarity of information, 94% of patients reported that they understood their test results at least to some extent (n=290) and 81% understood what their next steps were, at least to some extent (n=242). This compares favourably to the National Cancer Patient Experience Survey 2021 where just 78.8% understood their test results for any diagnostic tests. 10% (n=29) felt neutral on understanding their next steps, and 9% did not understand their next steps (n=26, disagree or strongly disagree)(NHS England, 2022a).

> *“It was okay as she wrote a letter, and it just said the cells on the Cytosponge have not shown any abnormality. This is good news. The symptoms running heartburn and he put me on a tablet.”*

Most patients had a clear understanding of the next steps in their pathway, but there were differences by result type and degree to which patients felt their problems were addressed.

Patients’ understanding of what their next steps were differed by result type. Most patients received a negative test result and were subsequently discharged. Of those with negative results, most patients recalled receiving directions for next steps following the results, which varied and included: continuing medication, changing medication, adjusting diet and lifestyle, and/or further tests. Most patients with negative results were happy with their next steps, however this also differed amongst those who were experiencing negative side effects from their reflux condition. Few patients with negative results did not feel their next steps were clear or felt they wanted more answers or direction to get to the root of their issues, rather than continuing interventions they’ve already tried. The method by which results were shared, even if negative, played a role for those experiencing uncomfortable symptoms. In these types of cases, the inclusion of further information or advice on what patients might do if symptoms persist could be considered with the communication of results.

> *“It'd been nice to, instead of just receiving a letter, I'd be brought back in to discuss the results. Then I could have turned around and said, “well, OK, that's fair enough. But I've still got the problem. Can you try and find out what it is?” Which then, I might have been put back on the list to have a camera or something.”*

> *“I think the main thing I understood was there was nothing untoward found so I kind of didn't pay that much attention. It was like clear.”*

> *“Yes. It was okay as she wrote a letter and it just said the cells on the Cytosponge have not shown any abnormality. This is good news.”*

Patients who had received a previous endoscopy were more likely to understand what steps they needed to take next compared to those who had not received a previous endoscopy (89%, n=87 vs 78%, n=153).

Patients who were referred for a subsequent endoscopy were more likely to understand to at least some extent what their next steps were after receiving their results (89%, n=77 of 87) compared to those who were not referred for an endoscopy (79%, n=161 of 205).

Patients who were referred for a subsequent endoscopy were more likely feel that their original issue was resolved, at least to some extent, (74%, n=67 of 90) than those who were not referred for an endoscopy (69%, n=147 of 213).

Patients who felt their original issue was resolved at least to some extent were also more likely to report that they understood what their next steps were (89%, n=188 of 209) compared to those who did not feel their original issue was resolved (61%, n=54 of 88).

> *“They said that there was no cancer cells so I wouldn't be getting a camera test, but I still get quite bad, acid reflux and stuff. So you know it would have been nice to know whether there was a hernia or something.”*

This sentiment also highlights that some patients did not realise what the Cytosponge test would or would not reveal.

Around two-thirds of patients self-reported their original issue was resolved as far as possible.

When patients were asked the extent to which they felt that their original issue was resolved as far as possible, 67% (n=222) of patients stated “yes, it definitely had”, or “yes, to some extent” (n=222), whereas 33% of patients indicated their issue had not been resolved as far as possible (n=109). Males were slightly more likely to report their original issue was resolved at least to some extent (72%, n=92) compared to females (64%, n=130). Patients who had previously had an endoscopy procedure were only slightly more likely to indicate their issue had been resolved to “some extent” or “definitely” (71%, n=82) compared to those who had not (65%, n=138).

Patients interviewed who indicated their original issue had not been resolved reported ongoing reflux issues in conjunction with a lack of understanding of the purpose of Cytosponge.

Evaluation Question 4: Patient inequalities

How does Cytosponge affect patient inequalities, both in access to a diagnosis and outcomes?

The below discussion focuses on observed differences in the Cytosponge diagnostic pathway (including patient test results and subsequent actions), waiting times, and endoscopy rates by levels of deprivation, sex, age, and ethnicity. This analysis is based on evidence drawn from the Impact Evaluation analysis and the Patient Experience survey.

Deprivation

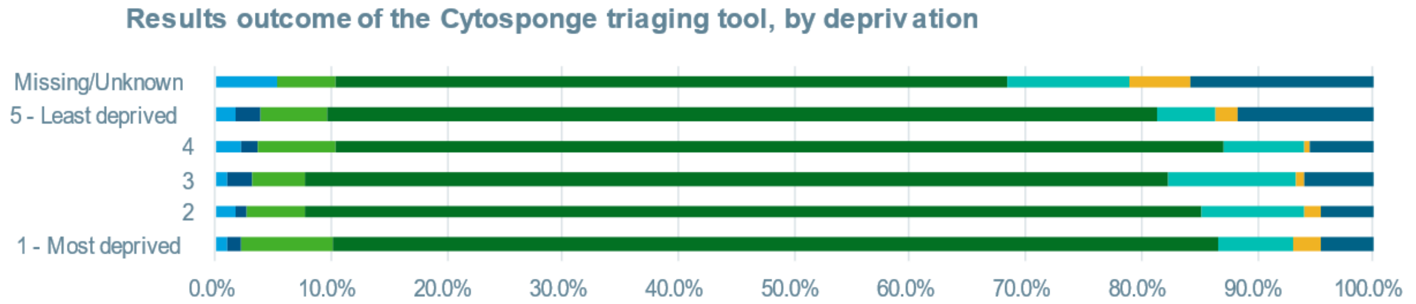
There was no clear evidence of inequalities in accessing a diagnosis, or differences in waiting times, based on levels of deprivation.

Amongst patients who successfully completed a Cytosponge test (n=1,411), the distribution of test results was similar across IMD quintiles (Figure 9). For example, 76.5% [95% CI: 70.8% to 81.4%] (n=202 of 264) of patients tested negative in the 1st IMD quintile (most deprived) compared to 71.7% [95% CI: 66.1% to 76.6%] (n=215 of 300) testing negative in the 5th IMD quintile (least deprived). However, the proportion of patients discharged or monitored was higher for the 1st IMD quintile with 63.6% [95% CI: 57.5% to 69.4%] (n=168 of 264) compared with the other quintiles, such as the 5th IMD quintile with 46.3% [95% CI: 40.6% to 52.2%] (n=139 of 300) (Figure 9). This may be suggestive of a health inequality, but those in the 5th IMD quintile were also more likely to have an unknown or “Other” subsequent action recorded. If patients with an “Other” or unknown subsequent action are assumed to be discharged, then the proportions of patients discharged are similar across IMD quintiles (for example 75.6% in the 1st IMD quintile (n=200 of 264) compared to 73.7% (n=221 of 300) in the 5th IMD quintile). Hence, given the unclear discharge status of these groups, no clear conclusions can be drawn regarding inequalities in accessing a diagnosis related to deprivation. More detailed data collection and longer-term follow-up to determine subsequent referrals would be required to further understand this.

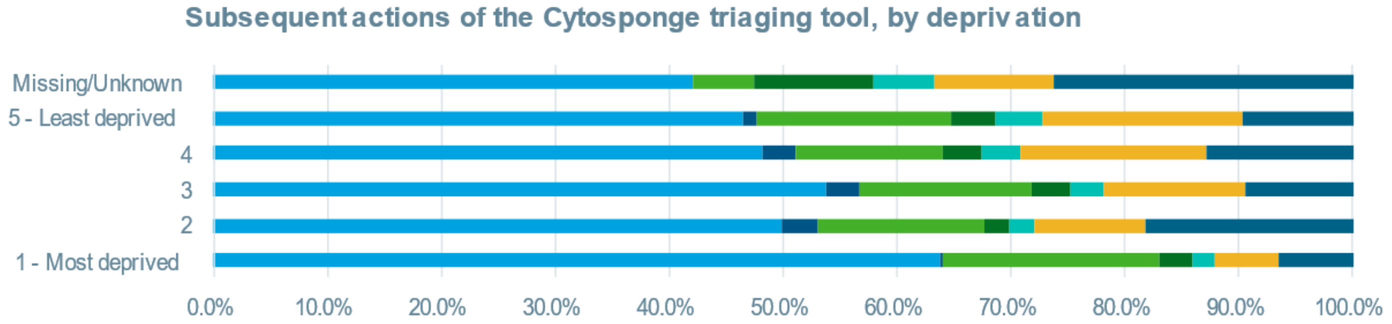
Further analysis of the subsequent actions of Cytosponge patients stratified by their test results within each IMD quintile supported the above. Amongst Cytosponge patients with a negative test result (n=1,060), a higher proportion of patients in the 1st IMD quintile (81.2%, [95% CI: 75.0% to 86.2%], n=164 of 202) were discharged/monitored compared to patients in the 5th IMD quintile (61.9% [95% CI: 55.0% to 68.3%], n=133 of 215). However, no formal statistical comparisons were conducted and as above, this difference was no longer present if the “Other” and unknown subsequent actions were also assumed to represent discharges (89.6%, n=181 of 202 in the 1st IMD quintile compared to 91.6%, n=197 of 215 in the 5th IMD quintile).

Furthermore, there were no clear differences by deprivation levels in the median time to the end of the diagnostic pathway amongst either Cytosponge or counterfactual patients. The median time from triage to the end of the pathway was approximately 48 days for Cytosponge patients across all IMD quintiles.

Figure 9. Amongst those who successfully completed the test, consequences of the Cytosponge triaging tool, by deprivation (i.e., IMD quintiles, n=1,411)



	1 - Most deprived	2	3	4	5 - Least deprived	Missing/Unknown
■ Atypia and/or abnormal P53	1.1%	1.8%	1.1%	2.2%	1.7%	5.3%
■ Atypia of uncertain significance or equivocal P53	1.1%	1.1%	2.2%	1.5%	2.3%	0.0%
■ TFF3 positive only	8.0%	4.9%	4.4%	6.7%	5.7%	5.3%
■ TFF3 negative + normal P53	76.5%	77.5%	74.7%	76.7%	71.7%	57.9%
■ TFF3 inadequate samples	6.4%	8.8%	11.0%	7.0%	5.0%	10.5%
■ TFF3 equivocal	2.3%	1.4%	0.7%	0.4%	2.0%	5.3%
■ Missing/Unknown	4.6%	4.6%	5.9%	5.6%	11.7%	15.8%



	1 - Most deprived	2	3	4	5 - Least deprived	Missing/Unknown
■ Discharge/monitoring	63.6%	49.8%	53.9%	48.2%	46.3%	42.1%
■ Re-test	0.4%	3.2%	2.9%	3.0%	1.3%	0.0%
■ Routine Endoscopy	18.9%	14.7%	15.0%	13.0%	17.0%	5.3%
■ Urgent Endoscopy	3.0%	2.1%	3.3%	3.3%	4.0%	10.5%
■ Endoscopy (unknown urgency)	1.9%	2.1%	2.9%	3.3%	4.0%	5.3%
■ Other	5.7%	9.8%	12.5%	16.3%	17.7%	10.5%
■ Missing/Unknown	6.4%	18.3%	9.5%	13.0%	9.7%	26.3%

Note. Results based on the unweighted Cytosponge cohort. Source: Impact Evaluation data.

Sex

There were similar proportions of test results and subsequent actions in men and women, which does not align with the expected higher risk of BO amongst men.

Approximately three-quarters of females and males (76.6% [95% CI: 73.5% to 79.4%], n=618 of 807 and 73.2% [95% CI: 69.4% to 76.6%], n=442 of 604, respectively) had a negative result. The proportion of patients with positive test results was similar across sexes, and there were no major differences in numbers of women and men referred for an endoscopy (routine, urgent or unknown urgency), with 20.7% [95% CI: 18.0% to 23.7%], (n=167 of 807) and 23.2% [95% CI: 19.9% to 26.8%], (n=140 of 604) respectively.

The risk of BO and other reflux-related disorders is higher amongst men than women (Fass et al., 2021). The similarity in subsequent actions observed across sexes could indicate the presence of a health inequality in access to a diagnosis for men, or similarity in test results could signify selection bias affecting the representatives of the Cytosponge group.

There were some differences by sex in the experiences of Cytosponge patients.

The most noticeable differences observed in the self-reported Patient Experience survey data are summarised below:

- Male respondents were more likely to report they strongly agreed that they were satisfied with Cytosponge test overall (59%, n=74) compared to women (45%, n=90).
- Male respondents were more likely to report they strongly agreed that they were happy to be offered Cytosponge instead of waiting for endoscopy (59%, n=75) compared to women (48%, n=96).
- Male respondents were less likely to report experiencing any pain during the test (27%, n=32) compared to women (42%, n=72).
- Female respondents were more likely to report experiencing discomfort in the days following their test (37%, n=72) compared to men (31%, n=39).
- Female respondents were more likely to report they were told they would be taken off the waiting list for endoscopy (43%, n=90) compared to men (32%, n=42).

Overall, these results suggest that men had a more favourable experience of the Cytosponge test compared to women. The above results have not undergone statistical significance testing, however statistical significance testing was carried out on key variables including sex and is available in a separate report.

Age

There was no evidence of inequalities related to age in access to diagnosis.

Amongst the 1549 patients who were offered Cytosponge, 36.2% were aged 18-45, whilst 21.8%, 23.2% and 14.5% were aged 46-55, 56-65 and 66-75 respectively. The high proportion of younger patients may have elongated the average time to end of pathway amongst Cytosponge patients, as they are more likely to need a confirmatory endoscopy to diagnose their reflux symptoms (Yamasaki et al., 2018). This is because reflux symptoms in younger patients (aged <45) are more likely to be caused by an underlying condition requiring an endoscopy, as opposed to atypia or TFF3 (detected by Cytosponge) (Yamasaki et al., 2018). Future service provision should consider the appropriateness of using this test for younger cohorts, as using Cytosponge in these cohorts could lead to elongating their diagnostic pathway by introducing an extra test.

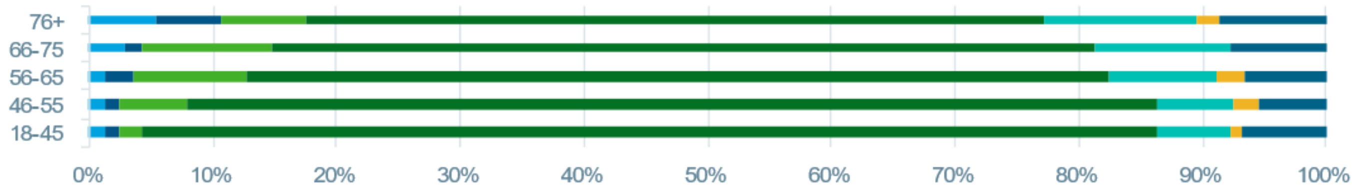
The proportion of patients with a positive result increased with older age groups (see Figure 10), from 4.2% (95% CI: 2.7% to 6.4%, n=21 of 503) in 18–45-year-olds to 17.5% (95% CI: 9.2% to 30.4%, n=10 of 57) in 76+ year olds. Correspondingly, a higher proportion of patients in the older age groups were referred for an onward endoscopy than the younger age groups, with 36.8% (95% CI: 24.7% to 50.7%, n=21 of 57) of 76+ year olds and 15.9% (95% CI: 12.9% to 19.5%, n=80 of 503) of 18–45-year-olds.

This trend was driven by the group of patients with a routine endoscopy referral. Less variation with age was observed amongst patients with an urgent referral, although this could be explained by the smaller size of the cohort of patients with urgent referrals. Furthermore, a lower proportion of patients in the older age groups were discharged or monitored, with 38.6% (95% CI: 26.3% to 52.4%, n=22 of 57) of 76+ year olds, compared to 54.5% (95% CI: 50.0% to 58.9%, n=274 of 503) of 18–45-year-olds.

Overall, these results suggest that the proportion of patients with a positive Cytosponge test result increased with older age, alongside a subsequent increase in endoscopy referrals. This indicates that older patients were at a higher risk of BO and were appropriately prioritised through the pathway. This is expected as the severity and incidence of BO and other gastroesophageal reflux disease complications increase with age (Chait, 2010). However, no formal comparative statistical tests were conducted due to the small sample sizes of this stratified analysis. Hence, the estimated proportions have wide CI, and differences may not be statistically significant.

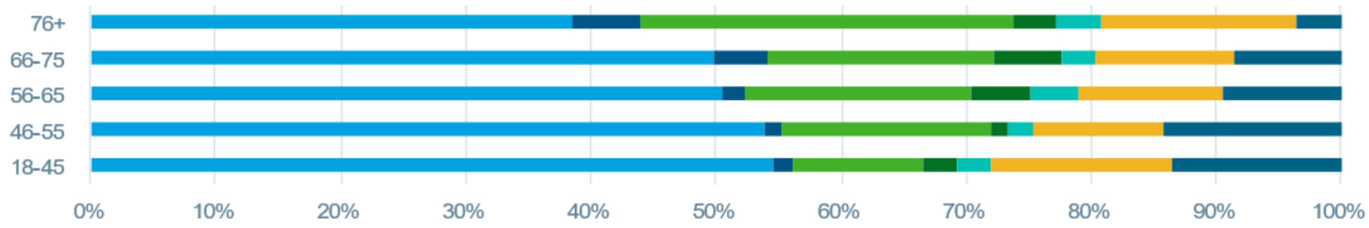
Figure 10. Amongst those who successfully completed the test, consequences of the Cytosponge triaging tool, by age (n=1,411)

Results outcome of the Cytosponge triaging tool, by age



	18-45	46-55	56-65	66-75	76+
■ Atypia and/or abnormal P53	1.2%	1.3%	1.2%	2.9%	5.3%
■ Atypia of uncertain significance or equivocal P53	1.2%	1.0%	2.4%	1.4%	5.3%
■ TFF3 positive only	1.8%	5.6%	9.2%	10.5%	7.0%
■ TFF3 negative + normal P53	82.1%	78.3%	69.7%	66.5%	59.7%
■ TFF3 inadequate samples	5.96%	6.25%	8.61%	11%	12.28%
■ TFF3 equivocal	0.99%	1.97%	2.37%	0%	1.75%
■ Missing/Unknown	6.76%	5.59%	6.53%	7.66%	8.77%

Subsequent actions of the Cytosponge triaging tool, by age



	18-45	46-55	56-65	66-75	76+
■ Discharge/monitoring	54.5%	54.0%	50.5%	49.8%	38.6%
■ Re-test	1.6%	1.3%	1.8%	4.3%	5.3%
■ Routine Endoscopy	10.5%	16.8%	18.1%	18.2%	29.8%
■ Urgent Endoscopy	2.6%	1.3%	4.8%	5.3%	3.5%
■ Endoscopy (unknown urgency)	2.8%	2.0%	3.9%	2.9%	3.5%
■ Other	14.5%	10.5%	11.6%	11.0%	15.8%
■ Missing/Unknown	13.5%	14.1%	9.5%	8.6%	3.5%

Note. Results based on the unweighted Cytosponge cohort. Source: Impact Evaluation data

Ethnicity

No robust conclusions regarding inequalities related to ethnicity can be drawn due to small sample sizes.

Due to small sample sizes in some ethnic groups, no conclusions could be drawn with confidence in terms of differences in test results and subsequent actions of Cytosponge by ethnicity. Similarly, amongst patients who completed the patient experience survey, there were only eight respondents who reported they were from a non-white background. As a result, comparisons by ethnicity are unlikely to be meaningful due to the lack of representation from non-white ethnic groups. Further monitoring and evaluation are required to explore patient inequalities in terms of ethnicity.

Overall, future service provision should continually be informed by patient inequalities to improve patient outcomes and access to care. It also remains important to continue monitoring whether future service provision is meeting the needs and delivering strong outcomes for all patients. Additional quantification of the role of health inequalities in the Cytosponge programme using larger samples of patients is needed to draw more robust conclusions.

Evaluation Question 5: Enablers and barriers

What are the barriers and enablers to the implementation of Cytosponge in secondary care?

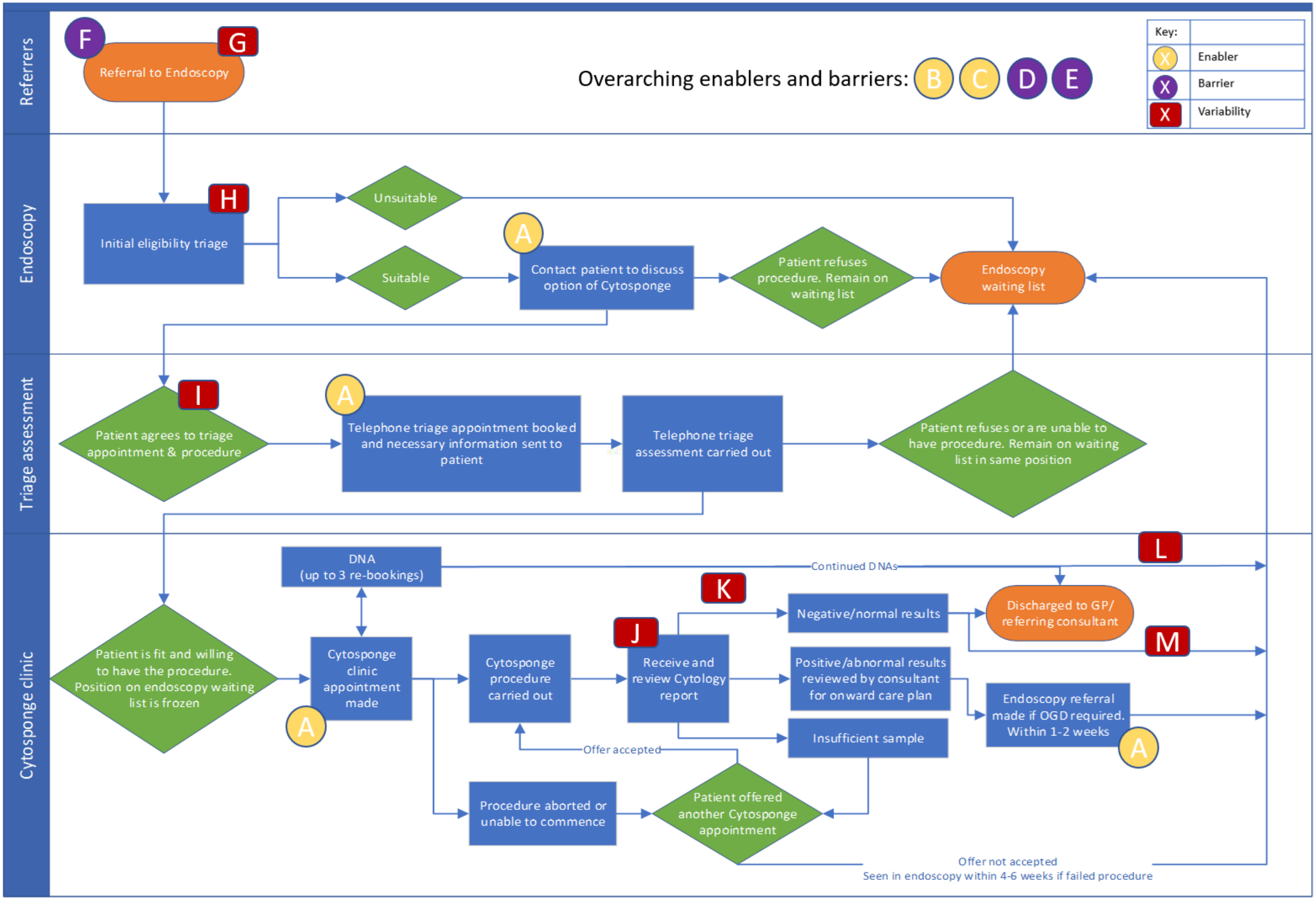
The below discussion on barriers and enablers is primarily drawn from analysis completed by the Process Evaluation workstream, supported by and triangulated against evidence from Patient Experience analysis. Priority points to emphasise include the success of NHSE in setting-up and delivering a complex and large-scale pilot service in such a short space of time (i.e., 3-months) and during the COVID-19 global pandemic, which created many challenges.

Key enablers and barriers were identified by NHS staff during discussions with them in all Cytosponge delivery sites and are highlighted across the patient pathway displayed in Figure 11.

This figure also illustrates where there are identified points of variability. Variability in patient pathways can hinder a consistent approach to a process but can also demonstrate the need for flexibility on a site-by-site basis.

This evaluation of the Cytosponge pilot programme considers all the barriers and enablers reported during the pilot phase. Not all of these will be relevant to a national roll-out (e.g., manual nature of data collection), but are considered in the evaluation as they had an impact on the Cytosponge teams and pilot programme implementation. Where these points are not relevant to a future national roll-out, this has been highlighted within the text.

Figure 11. Barriers, enablers, and variability highlighted across the Cytosponge patient pathway



Enablers

Enabler A: Dedicated Cytosponge administrative support enabled efficient delivery of services.

A dedicated Cytosponge team was deemed imperative for a successfully implemented, scalable, and sustainable service. This was reflected in both site- and programme-level perspectives.

The volume of administrative support required was believed to be unrealistic for clinical personnel to manage alongside their clinical duties. For sites with the available resources, having dedicated administrative support personnel during service set-up and throughout the service delivery allowed better management of contracting and delivery of services.

Managing contracting, coordinating procedures and establishing protocols required a high level of resources and time during site set-up and delivery of services. In some cases, a lack of support led to delays in site set-up. Specifically, administrative support was required at several pathway junctions. For instance, when contacting eligible patients, booking appointments (telephone triage and procedure appointments), distributing procedure information, arranging repeat appointments (for failed tests and DNAs) and arrangement of discharge or referral of administrative information.

MI analysis identified that there was generally a very high attendance rate for the test, with only 1.6% (n=42 of 2683) of those patients who accepted Cytosponge subsequently not attending the test. Reasons for non-attendance reported by NHS staff at the pilot sites were often related to booking issues: either the patient did not know that the appointment was booked; did not know how to cancel the appointment; or they did not receive confirmation of the appointment. Such issues are typically linked to administrative tasks. Therefore, it is possible that for those who experienced an unmanageable administrative burden, these booking issues could be related. This also highlights a possible area of improvement through use of technology to ensure it is clear for patients when an appointment is booked, ensure a booking confirmation is sent, and provide clarity on how to cancel an appointment.

Having administrative support personnel allowed clinical staff to focus on their clinical roles (e.g., triaging patients, delivering Cytosponge procedures, reviewing results, etc.) which created an environment conducive to the delivery of high-quality care.

Additionally, the sites that had adequate administrative support found the administrative burden associated with data collection (data required for NHSE insight and the pilot evaluation) far less intense than sites that did not have adequate administrative support. From both a site-level and a programme-level perspective, the ‘data collection’ referred to the completion of the Cytosponge forms, which required input of patient details and medical history, appointment details including details of the Cytosponge procedure, the results from the procedure and any subsequent action required for each patient. All individual patient data had to be manually collated into a master spreadsheet for subsequent transmission to IQVIA. This additional data collection was required from the beginning of the pilot to support a robust and comprehensive evaluation of the Cytosponge programme. This is unlikely to be as relevant in a national roll-out due to the lack of data requirements relating to the evaluation. However, its impact on staff during the pilot project should be acknowledged as one of the reasons why additional administrative support was deemed so crucial.

Recommendations for a national roll-out

A recommendation for the long-term and national roll-out was the creation of a clinical code for the Cytosponge procedure. It was suggested that this would enable the centralisation of patient counts for those receiving Cytosponge test, however, it may not allow for the capture of all granular data used in this evaluation. This recommendation has now been actioned by NHSE.

To conclude, the need for dedicated administrative support is deemed imperative. Administrative support will be needed throughout service set-up and delivery, but to a greater extent during set-up. It is advised that staff in such roles are provided with protected time to dedicate to Cytosponge duties, which should not just be regarded as an additional task to complete alongside and in addition to other roles.

Enabler B: A dedicated but flexible physical space for Cytosponge procedures made it easier for sites to deliver the service.

It was repeatedly expressed that a dedicated large multi-purpose room, with all required clinical (i.e., a trolly to hold and transport all Cytosponge kit, and an urn for warm water if in a room without a tap etc.) and administrative equipment, should be provided for clinical consultations and administrative work. However, the room required to carry out a Cytosponge test is not the same as the clinical room required for an endoscopy (i.e., ventilation). Therefore, there is more flexibility in the room options for Cytosponge compared to endoscopy resulting in the Cytosponge service being less complex to accommodate.

Staff and patients also expressed that Cytosponge may not "belong" in secondary care. Specifically, it was suggested that patients with routine reflux could receive Cytosponge in primary care.

> *"… get it done in your doctor surgery rather than going to the hospital and I thought that would be a win-win for everybody. Obviously, the doctor surgery is only like half a mile away rather than going over to the hospital and which is like a whole event, a lot more time."*

NHS staff involved in the pilots proposed that NHSE should consider providing Cytosponge for patients with routine reflux as a function in Community Diagnostic Centres (CDCs). The suggestion of providing a low-risk procedure via CDCs for low-risk patients with routine reflux was mainly for the Cytosponge team to retain the staff experience required for triage (i.e., secondary care endoscopy nurses). Patients interviewed also supported treatment closer to home.

> *"It just might be nicer to have it somewhere closer. I had it at the <hospital name removed> and it's 45 minutes from where I live, and it was in COVID, so I had to go over there twice, once to have the COVID test and then again for the Cytosponge test, but it was all very smooth and the staff were all brilliant."*

However, it was noted that there may be several logistical considerations if taking Cytosponge into the community, such as the requirement to be within a certain distance of an endoscopy unit, and the transfer of patient notes (if not electronic).

Recommendations for a national roll-out

A dedicated clinical (i.e., for Cytosponge procedure) and administrative (i.e., for telephone triage, correspondence etc) space for the Cytosponge team was recommended as being essential for a national roll-out. This would not only provide the physical space needed, but also the sense of purpose and belonging. For instance, if the Cytosponge service is within the endoscopy unit, some respondents reported wanting to feel more included, rather than segregated as a separate service. The suggestion regarding NHSE moving routine reflux patient Cytosponge services to CDCs is currently being explored further with stakeholders across primary, secondary and community care settings. NHSE launched this pilot in February 2023.

Enabler C: A dedicated, empathic, and experienced Cytosponge clinical team enabled more efficient and high-quality delivery of services.

A dedicated, empathic, and experienced Cytosponge nurse, an enthusiastic and involved Consultant, and dedicated administrative support personnel were the types of roles that enabled the most efficient and high-quality delivery of services.

The most experienced nurses were knowledgeable regarding endoscopy services and exhibited the most confidence delivering the Cytosponge procedure. This supported the delivery of high-quality patient care.

The quality of care from the Cytosponge nurses was repeatedly reported by patients.

> *"I really couldn't fault the interaction between the people carrying out the test and myself. It's what you hope the NHS would deliver. The whole procedure was done in a very caring kind of way with me as a person, taking into consideration I didn't feel as if I was just, you know, a guinea pig. Let's try this out kind of thing. I felt as if I was treated as a human being."*

It was suggested at a few deep-dive sites, as well as at the open-insight workshops, that more flexibility be provided in relation to how Cytosponge teams are resourced. For instance, a band 5 nurse being employed to work alongside an experienced band 7 nurse to carry out Cytosponge administration. Some interviewees suggested that a more experienced nurse is required for some tasks (e.g., triage assessments), but a less experienced nurse would be more than capable to carry out other clinic tasks. NHSE reported that funding was provided for a band 7 nurse at all sites to ensure an appropriately experienced nurse was able to run a Cytosponge clinic independently. Furthermore, anyone above a band 7 was able to deliver Cytosponge clinics, but no additional funding was provided. This resulted in one site dropping out of the pilot because the most suitable member of staff to run the clinic was a band 8 but this was not funded.

Recommendations for a national roll-out

For a national roll-out, it is advised that a dedicated and experienced Cytosponge clinical team is essential. An experienced Cytosponge clinical team would likely consist of staff who have a background in endoscopy or upper Gastrointestinal (GI) conditions, have the necessary confidence and experience of working in a smaller team, and with putting patients at ease with a new procedure. NHSE did provide funding for staff time to set-up and carry out the Cytosponge service, but evidence from this evaluation shows that providing funding does not always lead to the equivalent and expected time spent on the required duties. For instance, in some sites, staff worked more than their allocated hours, primarily due to the reported administrative load, particularly during the set-up phase and evaluation data collection phase. However, some sites experienced some staff not engaging as much as would be expected. For instance, in two sites, the clinical leads were not engaged in the Cytosponge service unless absolutely necessary. As per enabler A, it is advised that staff in Cytosponge roles are provided with protected time to dedicate to Cytosponge duties so that it is not just regarded as an additional task to complete alongside another (main) role, which may supersede such duties.

Barriers

Barrier D: Lack of awareness of specific guidance created barriers in site set-up.

A lack of awareness regarding specific guidance created additional effort required by sites. At a programme-level, it was acknowledged that the provision of specific and targeted support and guidance was a challenge due to the greater than expected number of pilot sites involved, thus offering less opportunity to provide tailored support to individual sites. In addition, the inaccuracy of patient number predictions at service set-up was a challenge to the development of suitable resourcing. There was also some confusion about the role of the Cancer Alliance in a possible future national roll-out of Cytosponge.

Furthermore, sites reported a lack of awareness regarding who could support them within their trust when needing to sign-off on a data sharing agreement (DSA). Sites with a small or no dedicated administrative teams were much more susceptible to delays in site set-up. Sites had the opportunity to attend 1:1 workshop with IQVIA to support with sign-off of their DSA. Despite the support and guidance provided, some sites were still unable to identify the appropriate individuals to sign-off on these contracts. However, data collection and the requirement for a DSA was specific to the set-up process of the pilot project and is unlikely to be an issue in a national roll-out as sites will not need to share evaluation data or sign a DSA.

Recommendations for a national roll-out

For a national roll-out, it is advised that NHSE ensure appropriate support is available to sites and that peer support links between new and established sites are created. NHSE should clarify the role of the key stakeholders, e.g., Cancer Alliances, in a national roll-out and work with stakeholders to create accurate predictions on the potential patient numbers and resourcing required.

Barrier E: The need to conduct site-by-site contracting and key document creation and sign-off created additional workload during set-up, which not all sites were prepared for.

The need to conduct site-by-site contracting and key documentation creation and sign-off generated a significant additional workload, which sites were not prepared or resourced well enough for. Most reported site-level contracting issues were related to typical HR and local procurement challenges specific to each trust. Most sites reported that the contracting process was complex and that they had to develop much of the required documentation from scratch. NHSE provided the templates required for the development of policies and procedures, for example, but it seemed some trusts were not aware that they were provided and therefore struggled to develop their own. Sites reported feeling overwhelmed by the volume of information provided during the set-up phase and this may have affected their awareness of the templates available.

The individuals typically involved in the additional workload (e.g., clinician/nurse) were clear that their priority tasks whilst at work were their clinical duties, especially during the COVID-19 pandemic. Whilst the necessary administrative tasks required during the set-up phase may not have seemed too onerous, they were a significant burden on the staff, especially when clinical need was of greater urgency.

> *"I am a nurse, I am not trained or meant to be doing this sort of thing. My main priority are my patients, not paperwork".*

Recommendations for a national roll-out

If contracting was managed centrally, or by a dedicated administrator, this would reduce much of the administrative burden and would accelerate the set-up phase. Unfortunately, the central management of contracting is a rarity and whilst ensuring the suggestions of the respondents are not discounted, the more pragmatic approach would be to suggest involving local procurement teams from each trust earlier in the contracting process.

Barrier F: Lack of knowledge, education, guidance, and therefore confidence in Cytosponge test results was a barrier.

Following a Cytosponge test, clinicians review and refer patients for an onward endoscopy on a case-by-case basis and make clinical judgements where appropriate. Discussions with clinicians indicated that a lack of knowledge, education, guidance and, therefore, confidence in Cytosponge test results influenced the application of the Cytosponge clinical guidelines. This led to some cases of patients being referred for an onward endoscopy following a negative Cytosponge test, or incomplete/TFF3 equivocal test, instead of a Cytosponge repeat test. This is also seen in the findings for Evaluation Question 1, which show that 22% of patients who received a Cytosponge were referred for an onward endoscopy, whereas only 8.6% had a positive test result in the Cyted results.

> *"We cannot be completely sure that the patient is not experiencing symptoms of something more sinister when just using a Cytosponge, so yes, we would still usually send them for an OGD if we need reassurance."*

It is important to note that a lack of clinician confidence was not the only reason why there was a discrepancy between the number of patients referred for endoscopy compared to the number of positive test results. The clinical guidance provided Cytosponge teams the ability to make a case-by-case judgement for each patient. This included, for instance, patients with negative test results, but persistent symptoms were to be referred for endoscopy. Interestingly, onward referrals for patients with a negative Cytosponge test decreased over the pilot period. This suggests the clinical confidence may have increased with more use of the test and evidence of outcomes (e.g., safety and efficacy).

Recommendations for a national roll-out

Efficiencies in the pathway and further reduction in ongoing referrals to endoscopy seem possible by addressing clinician confidence in Cytosponge test results. This could be done through sharing Cytosponge data, improvements in education and knowledge of using Cytosponge as a triaging tool and the application of the clinical guidance. An education programme on Cytosponge across primary, secondary and community care is recommended for a national roll-out.

Variability

Specific points where variability in the patient pathway occurred was noted on the pathways map as red rectangles labelled with letters G – M (see Figure 11). The following points provide additional context around each area variability identified in the Process Evaluation:

- **Variability Point G**: Some sites had direct GP referrals set up, but most patients either came from the main endoscopy waiting list or internal clinics (e.g., gastroenterology).

- **Variability Point H:** Sites showed a mix of both consultant led and nurse led triage. One site did not carry out an initial eligibility triage, they just booked all patients on the waiting list into the telephone triage clinic. All other sites carried out an initial eligibility triage whereby a clinician would typically scan through the referrals to highlight all those who may be suitable for Cytosponge.

- **Variability Point I:** Most sites had routine triage clinics set up, but some carried out this step in the pathway on an ad-hoc basis. Again, this may be due to more (or less) patient numbers than expected. Routine triage clinics would usually be set days/times blocked out each week.

- **Variability Point J:** Pathology reports were mostly reviewed by the consultant. Some were nurse reviewed and only passed onto the consultant if the results were positive, abnormal or failed.

- **Variability Point K:** There were a range of ways on which results were communicated (i.e., phone, letter, email etc.). In some situations, the communication methods were dependent on the result, e.g., positive, abnormal or failed results were reviewed and followed-up by the consultant Negative/normal results were communicated by the nurse.

- **Variability Point L:** After 2-3 non-attendances, some sites would discharge the patient back to the GP or referring consultant, and others would reinstate their position on the endoscopy waiting list.

- **Variability Point M:** Most patients who received a negative/normal Cytosponge test result were discharged to the GP or referring consultant. However, it was also reported that patients with a negative/normal test result, but with persistent symptoms, were referred through to endoscopy.

Variability can be seen as a positive in some instances due to the flexibility required when trying to implement change in heterogeneous settings (e.g., an experienced clinical nurse specialist could carry out the triage review in some sites, but in others, it would need to be the consultant). However, variability could also be viewed as a negative in the same situation. For instance, a consultant may be needed for the triage review, but may not be appropriately engaged in the service and therefore the nurse carrying out the triage review may experience a lack of confidence in their judgement and would greatly value a consultant’s view.

Evaluation Question 6: Cost effectiveness

What is the cost-effectiveness and budget impact of Cytosponge, when used as a diagnostic triage tool in secondary care?

The discussion below focuses on the cost-effectiveness and budget impact of Cytosponge from the perspective of the NHS in England, based on the analysis conducted by the Health Economics Evaluation workstream. Detailed analyses (e.g., sensitivity/scenario analyses results) that supports these findings are provided in a technical report, separate to this document. The definitions of specific terms used in the economic analysis in this section are provided in the Health Economics Evaluation methodology description in Section 2.

Cost effectiveness model

Including Cytosponge in the diagnostic pathway is highly cost-effective relative to an endoscopy-only programme, resulting from a moderate cost-saving relative to a minimal reduction in quality adjusted life years (QALYs).

In the cost effectiveness model (CEM) base case, the Cytosponge programme results in a per-patient cost-saving of £421.57 and a very slight decrease in QALYs of 0.0041 (Table 11). Expressed differently, the endoscopy-only programme’s health utility improvement relative to the Cytosponge programme carries an incremental cost per QALY of £102,188, which considerably exceeds the current willingness-to-pay (WTP) threshold of £20,000 per QALY.

Put another way, at a WTP of £20,000, the per patient Net Monetary Benefit (NMB) of the Cytosponge programme relative to the endoscopy-only programme is £339.06. Using weighted summary data (from the Impact Evaluation) in the Cytosponge arm, the results are similar in terms of total costs and QALYS accrued but result in a significantly larger ICER (£1,848,303/QALY) and NMB (£501.11). This results from a smaller incremental QALY value, and larger incremental cost value, relative to the base case.

Table 11 Base case cost-effectiveness results Cytosponge (full model)

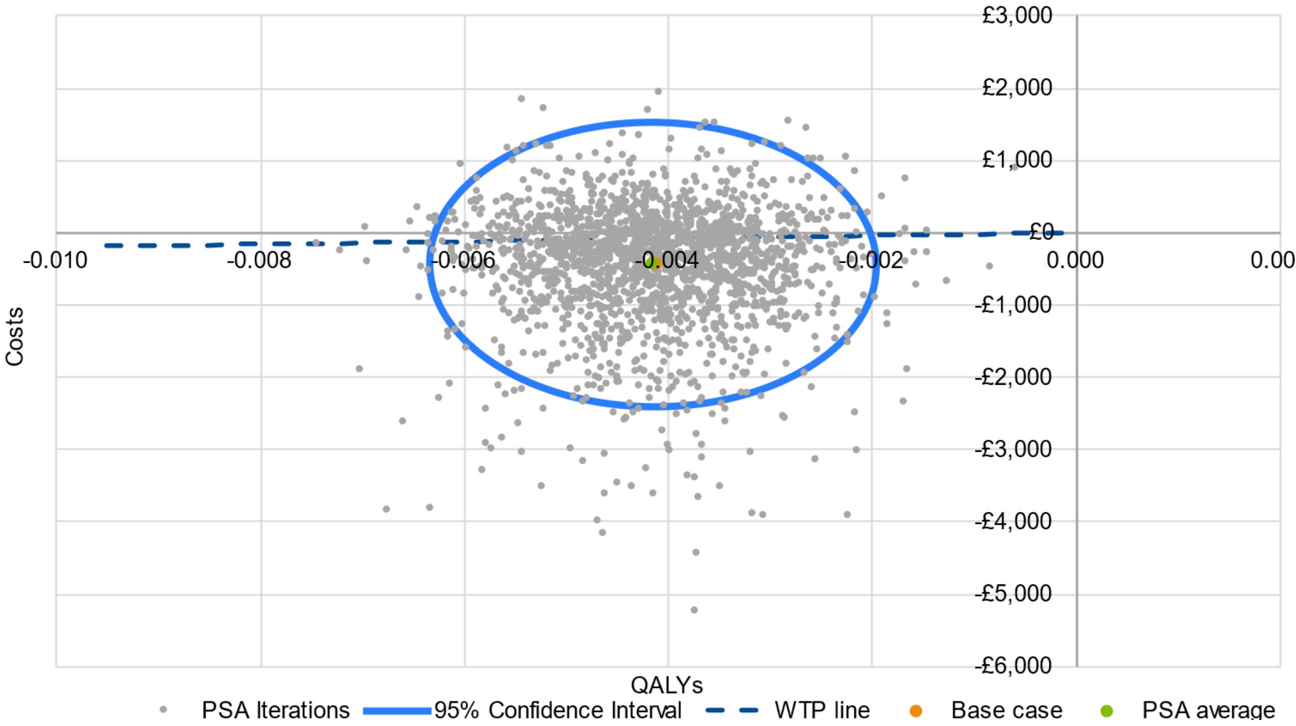
Outcome (per patient)	Endoscopy-only	Cytosponge	Incremental
Total LYs	18.9241	18.9218	-0.0023
Total QALYs	14.5578	14.5537	-0.0041
Total costs	£10,279.52	£9,857.94	-421.57
ICER (cost/LY gained)	£186,008.23 (Endoscopy-only relative to Cytosponge)		
ICER (cost/QALY gained)	£102,187.76 (Endoscopy-only relative to Cytosponge)		
NMB (WTP=£20,000/QALY)	£339.06		

Abbreviations: ICER: Incremental cost-effectiveness ratio; LY: Life years; NMB: Net monetary benefit; QALY: Quality-adjusted life year; WTP: Willingness to pay

Model results are robust in the presence of uncertainty: Cytosponge is generally cost-effective in sensitivity analyses.

Figure 12 provides the probabilistic sensitivity analysis (PSA) results in a cost-effectiveness plane, showing that most (71.2%) iterations of the PSA produce results in the south-western quadrant. This means that although there is a very slight marginal reduction in QALYs there are also moderate cost savings in the Cytosponge-arm compared to the endoscopy-arm.

Figure 12. Cost-effectiveness plane for Cytosponge vs endoscopy-only (incremental costs versus incremental QALYs)



Abbreviations: PSA: Probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: Willingness-to-pay.

The cost-effectiveness acceptability curve (CEAC) displayed in Figure 13 shows that at a WTP threshold of £20,000/QALY, the Cytosponge programme has a ~65% probability of being cost-effective; at a WTP of £30,000/QALY, the Cytosponge programme has ~63% probability of being cost-effective. Compared to endoscopy-only, the Cytosponge programme remains the more cost-effective option up until a WTP of £74,000/QALY.

Figure 13. Cost-effectiveness acceptability curve for Cytosponge vs endoscopy-only

The one-way-sensitivity analysis (OWSA) conducted, varying model parameters by +/- 20%, show that the costs of endoscopy testing and Cytosponge testing are the key drivers of the model results. For example, increasing the base case health resource group (HRG) cost of an endoscopy by 20% (from £878.00 to £1053.60) increases the NMB of the Cytosponge programme from £339.06 in the base case to £476.84 (given a WTP of £20,000/QALY). Decreasing the acquisition cost (adjusted for completion rate) of Cytosponge from £301.43 to £241.15 increases the NMB of the Cytosponge programme from £339.06 to £406.08.

The other key drivers of model results include the completion rate of Cytosponge (which is a factor in the acquisition cost of Cytosponge), the health state utility of the 'NO BO' health state, the sensitivity of Cytosponge, and the cost of the outpatient appointment required (in addition to the HRG cost of an endoscopy) during endoscopy testing. Of note, all results remain cost-effective in all parameter tests.

The key driver of the cost saving is the difference in the per-patient cost of diagnostic testing during the diagnostic pathway resulting from the avoided endoscopies in the Cytosponge-arm.

The major cost differences relate to the cost of endoscopy testing, and the cost of adverse events related to endoscopy testing, occurring during the diagnostic pathway. In line with the reduced demand for endoscopies in the Cytosponge arm, the per-patient cost of endoscopy testing is significantly lower in the Cytosponge arm during the diagnostic pathway (£198.77 vs £1,003.98). This difference, in addition to the lower cost of endoscopy-related adverse events during the diagnostic pathway (£32.08 vs £162.01) sufficiently offsets the per-patient cost of Cytosponge testing (£430.94) and drives the overall cost saving.

For all other costs differences in both the diagnostic and post diagnostic periods, the cost differences are insignificant. This reflects the fact that the other costs are generally dependent on health states but not dependent on arm. Also, the quality-adjusted time spent in each health state, in each model phase, is similar in each arm. In turn, these costs are similar across arms.

Varying the price of the Cytosponge has a significant effect on cost-effectiveness outcomes.

As discussed above, the price of the Cytosponge test was a main driver of cost-effectiveness results. The OWSA showed that, at a WTP threshold of £20,000/QALY, decreasing the price of the Cytosponge device by 20% (from £301.43 to £241.15) increases the NMB of the Cytosponge programme by 20% (from £339.06 to £406.08) and the ICER by 16% (from £ 102,188.19 to £ 118,431.90). Further analysis showed that this relationship was linear and consistent; that is for every 1% decrease in the price of Cytosponge, the NMB increased by 1% and the ICER by 0.8%. This shows that a reduction in in the price of the Cytosponge test results in an improvement in cost effectiveness results that is inversely proportional. Of note, this also means that an improvement in the Cytosponge test price results in a proportional reduction in the cost-effectiveness of the Cytosponge programme; however, the Cytosponge programme remains cost effective at all price points below £606.45.

The difference in QALYs between the Cytosponge and endoscopy-only programme is minimal.

The breakdown of QALY outcomes separated by health states in the base case shows slightly less (0.0008) QALYS accrued in the endoscopy-only arm during the diagnostic pathway, resulting from the dis-utilities (the value of the loss in the quality of life) associated with endoscopy testing. In the post-diagnosis period, there are slightly more (0.0049) QALYs accrued in the endoscopy-only arm resulting from an improved health state distribution, upon entry into the post diagnosis phase. The improved health state distribution upon entry reflected assumptions of a shorter time to diagnosis (46 days) and higher (perfect) sensitivity in the endoscopy-only arm. However, overall, there is a difference of 0.0041 QALYs between programmes – this is equivalent to a difference of 1.5 days. Furthermore, scenarios in which longer-time-to-diagnosis values (73.8, and 126) in the endoscopy-only arm were considered further reduced the QALY difference across programmes (0.003 and 0.0002 respectively). Assuming both an equal time to diagnosis *and* equal (perfect) sensitivity across both arms (i.e., equal efficacy) resulted in a *gain* in QALYs of 0.0008 in the Cytosponge arm compared to the Endoscopy-only arm.

A cost-minimisation scenario shows an improved cost saving in the Cytosponge programme relative to the base case.

Given the marginal difference between QALYs accrued, a cost-minimisation analysis (CMA) was conducted assuming equal efficacy, and thus life years accrued, between arms. This was done by assuming the same time-to-diagnosis, and sensitivity as in the endoscopy-only programme. This resulted in a cost saving of £526.39 relative to the endoscopy-only programme, increasing the cost saving in the base case cost-effectiveness analysis (CEA) (£421.57). This can also be understood as a NMB of £526.39 (compared to £339.06 in the base case). As in the CEA, the difference in costs is driven by the difference in per-patient diagnostic testing costs during the diagnostic pathway.

Following patient diagnostic pathway guidance results in a small increase in cost-effectiveness.

The findings for Evaluation Question 1, show that patients were not always assigned to a subsequent action in line with guidance. For example, 22% of patients who received a Cytosponge were referred for an onward endoscopy, whereas only 8.6% had a positive test result in the Cyted results. The Health Economics analysis showed that if clinicians assigned patients in the Cytosponge arm to a subsequent action in line with the guidance, this would increase the NMB from £339.06 to £361.09 (at a WTP of £20,000/QALY). This is consistent with the findings in Evaluation Question 1 which suggest a similar reduction in endoscopy demand with and without variations in patient diagnostic pathways (81% and 79% respectively). However, while the overall reduction in endoscopy demand was slightly smaller (79% vs 81%) in the scenario analysis, cost-effectiveness was slightly improved (£361.09 vs £339.06); because while the cost of endoscopy provision was similar in either case the health benefits of endoscopy provision were sufficiently improved in the scenario analysis (due to a sufficient improvement in the number of patients with a positive/uncertain Cytosponge completing an endoscopy in this scenario).

Of note, consistent with the approach used in the Impact Evaluation, in the base case, the health economic analysis did not account for patients with missing endoscopy records in the count of the number of patients completing an endoscopy. Assuming all patients referred for endoscopy did indeed complete an endoscopy, the resulting NMB is £299.88. Under this assumption, if clinicians assigned patients in the Cytosponge arm to a subsequent action in line with the guidance, this would increase the NMB from £299.88 to 361.09. This is in line with the findings in Evaluation Question 1 which show a reduction in endoscopy demand of 73% and 79% respectively with and without variations in patient diagnostic pathways if the same assumption is made. Under this assumption, the reduction in endoscopy demand is greater in the scenario analysis (79% vs 73%) resulting in a reduction in costs in the Cytosponge arm. However, health benefits are similar since all patients with a positive/uncertain result are considered to have completed an endoscopy in either case. Thus, there is an improvement in cost-effectiveness, and an improvement that is greater than under base case assumptions.

Given that the data underpinning this analysis is from the pilot, the expectation is that over time, post introduction of Cytosponge on a national scale, protocol adherence would tend towards optimal levels, and cost-effectiveness would increase further.

Additional key scenario analyses were tested in the health economic evaluation. Namely, the aforementioned “equal efficacy” analysis which was the most impactful scenario in terms of cost -effectiveness. It resulted in both higher QALYs (a small increase of 0.0008) and lower costs (by £526.39) in the Cytosponge programme, and therefore an NMB of £542.38 (compared to £339.06 in the base case). The inclusion of endoscopy re-tests also improved the cost-effectiveness of the Cytosponge programme: assuming an endoscopy re-test rate of 5% and 10% resulted in an NMB of -£385.70 and £432.33 respectively.

Budget impact model

The 5-year net budget impact of introducing Cytosponge is a budget saving of between ~£10 million and ~£33 million.

The budget impact model (BIM) is based on an incident eligible population of 15,121 in year 1, increasing to 17,019 by year 5, resulting in a cumulative incident population across the 5 years of 80,278 (Table 12). These figures are estimated based on data from the pilot programme and from NHS diagnostic waiting times and activity (see also Section 2).

Table 12 Budget impact model: patient trace

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Incident number of eligible patients	15,121	15,574	16,042	16,523	17,019	80,278

Abbreviations: GBP: Great British pounds.

Assuming the initial share of the population assigned to Cytosponge in year 1 is 10%, with an increase of 10 percentage points every year, the total spend in the ‘world with Cytosponge’ (WWC) is £215,647,300. The total spend in the ‘world without Cytosponge’ (WWoC) is £225,945,098. This results in a net budget saving over 5 years of £10,297,798.

Table 13 Base case budget impact results (GBP), assuming 10% initial share of patients in Cytosponge programme

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Net Budget Impact	-£637,691	-£1,308,046	-£2,017,920	-£2,769,490	-£3,564,650	-£10,297,798
World without Cytosponge	£29,259,592	£37,003,744	£44,948,536	£53,142,169	£61,591,057	£225,945,098
World with Cytosponge	£28,621,901	£35,695,698	£42,930,616	£50,372,678	£58,026,407	£215,647,300

Abbreviations: GBP: Great British pounds.

Assuming the initial share of the population assigned to Cytosponge in year 1 is 50%, with an increase of 10 percentage points every year, the total spend in the WWC is £202,196,679. The total spend in the WWoC is £225,945,098 (it is the same in every scenario as the endoscopy-only programme is the only available programme in this world). This results in a net budget saving over 5 years of £23,748,419.

Table 14 Base case budget impact results (GBP), assuming 50% initial share of patients in Cytosponge programme

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Net Budget Impact	-£3,188,457	-£3,912,943	-£4,700,450	-£5,533,621	-£6,412,948	-£23,748,419
World without Cytosponge	£29,259,592	£37,003,744	£44,948,536	£53,142,169	£61,591,057	£225,945,098
World with Cytosponge	£26,071,136	£33,090,801	£40,248,086	£47,608,548	£55,178,108	£202,196,679

Abbreviations: GBP: Great British pounds.

Assuming the initial share of the population assigned to Cytosponge in year 1 is 90%, with an increase of 10 percentage points every year, the total spend in the WWC is £192,951,102. This results in a net budget saving over 5 years of £32,993,996.

Table 15 Base case budget impact results (GBP), assuming 90% initial share of patients in Cytosponge programme

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Net Budget Impact	-£5,739,222	-£6,517,840	-£6,706,453	-£6,910,045	-£7,120,436	-£32,993,996
World without Cytosponge	£29,259,592	£37,003,744	£44,948,536	£53,142,169	£61,591,057	£225,945,098
World with Cytosponge	£23,520,370	£30,485,904	£38,242,083	£46,232,124	£54,470,621	£192,951,102

Abbreviations: GBP: Great British pounds.

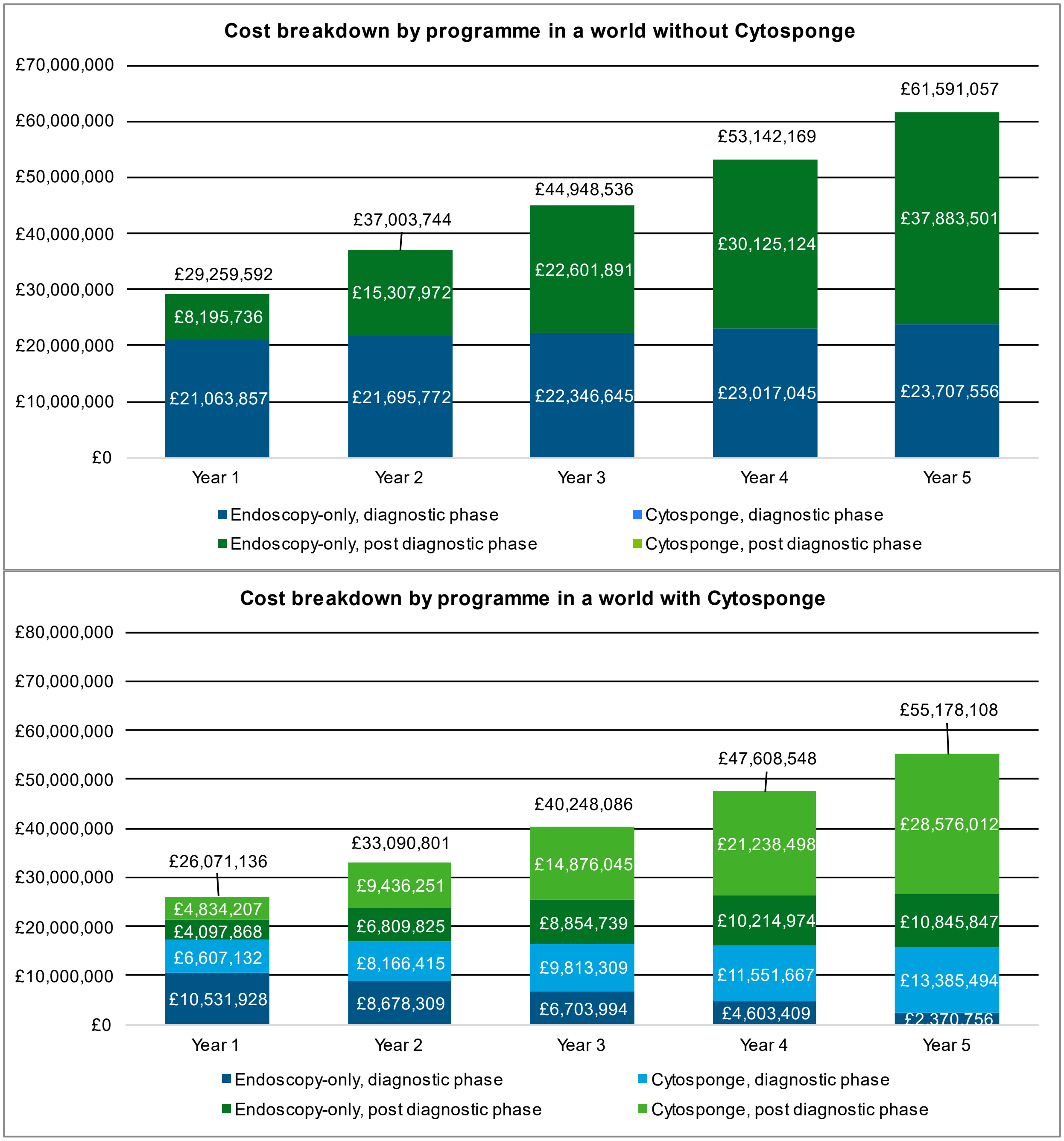
In each scenario, there is a budget saving of introducing Cytosponge in each year of the 5-year period, and the budget saving increases year-on-year resulting in a budget saving of between ~£10 million and ~£33 million.

Consistent with the cost-effectiveness analysis, budget savings are driven by the reduction in per-patient diagnostic testing costs during the diagnostic pathway in the world with Cytosponge.

For a scenario in which there is an initial 50% share of the population assigned to the Cytosponge programme, the breakdown of costs by programme and phase (diagnostic pathway phase and post diagnosis pathway phase) is provided in Figure 14. This shows that the cost difference is driven by the difference in costs during the diagnostic phase, which, in turn, are driven by the costs of diagnostic testing. In this scenario, this results in a cost saving of approximately £4,000,000 in year 1, during the diagnostic pathway; this saving increases annually (by roughly £1,000,000 per year) as the share of patients assigned to the Cytosponge programme increases annually.

Sensitivity analyses also confirm the inference that the key driver of results are diagnostic testing costs.

Figure 14. Base case budget impact results breakdown by phase (GBP), assuming 50% initial share of patients in Cytosponge programme



Abbreviations: GBP: Great British pounds.

Consistent with the cost-effectiveness analysis, varying the price of the Cytosponge has a significant effect on budget impact.

The OWSA showed that, at a WTP threshold of £20,000/QALY, decreasing the price of the Cytosponge device by 20% (from £301.43 to £241.15) increases the net budget impact of a world with Cytosponge by 16% (from a £24 million saving to a £28 million saving). This relationship was linear and consistent; that is for every 1% decrease in the price of Cytosponge, the budget saving increased by 0.8%. Furthermore, the Cytosponge programme remains budget saving at all price points below £678.42.

Consistent with the effect on endoscopy demand, scenario analyses show that having few or no variations on patient pathways has a small effect on budget savings.

Scenario analysis shows that assuming clinicians assign patients in the Cytosponge arm to a subsequent action strictly according to protocol has a small effect on budget impact. Based on a starting share of 50%, the assumption of no variations in patient diagnostic pathway results in a small *decrease* in the cumulative budget saving from £23,748,419 in the base case to £23,022,673. This is consistent with the findings in the Evaluation Question 1 which show that the reduction in endoscopy demand is slightly smaller in this scenario analysis compared to the base case (79% vs 81%), and thus the budget savings related to endoscopy avoidance are slightly smaller in this scenario analysis. This is inconsistent with the CEA in which there is marginal improvement in NMB when this scenario is applied. This is because, unlike the CEA, the BIM does not account for the utility of improved health; it is purely an assessment of financial impact. BIM results are therefore more likely to be directly proportional to variations in costs or resource-use, as is the case here.

Of note, if in the base case patients with a missing endoscopy record are included in the number of patients completing an endoscopy, the cumulative budget impact would be £21,124,182. This means that no variations in the patient diagnostic pathway would result in an increased budget saving (from £21,124,182 to £23,022,673. This is consistent with the Impact Evaluation findings which show a larger reduction in endoscopy demand in the scenario analysis compared to the base case (79% vs 73%) if this alternate method of calculating avoided endoscopies is used in the base case.

As with the CEA, the other scenarios that have the most impact, relatively, include the assumption of equal efficacy across arms, and increasing the rate of endoscopy re-tests.

With respect to the limitation of the BIM, it was not possible to provide a point estimate of results given the lack of evidence regarding service provision mix assumptions. However, it is clear that the Cytosponge programme is likely to be cost saving irrespective of the service provision mix scenario. Similarly, the method for calculating the eligible incident population suffers from a lack of data, and accuracy may be compromised based on the time from which the data is derived – that is, during the COVID-19 pandemic. However, here also, the BIM results were robust against alternative assumptions. Any future updates to this analysis based on improved data inputs in these areas may change the magnitude of the result but are unlikely to change the direction of results.

Evaluation Question 7: National roll-out

What resources would be required for roll-out of Cytosponge as a triage tool in secondary care?

This section addresses what resources and/or capabilities are recommended to maintain or improve the services provided in the pilot and in a future roll-out of Cytosponge. It also applies a ‘scalability model’ to understand potential costs of resources needed to run a future rolled-out Cytosponge programme.

Effective service delivery must be supported by a dedicated and experienced Cytosponge clinical team as well as dedicated administrative support staff.

Analysis to address Evaluation Question 5 highlighted that the most impactful enablers of effective Cytosponge service delivery were the availability of a dedicated, empathic, and experienced Cytosponge nurse, an enthusiastic and involved Consultant, and dedicated administrative support personnel, all with protected time in the service (see Evaluation Question 5 for further details).

Key areas of experienced expertise deemed necessary were staff who had a background in endoscopy, confidence in working in a smaller team, and ability to put patients at ease with a new procedure.

A preference for which method was used to communicate Cytosponge results (e.g., telephone or letter) back to the patient was identified (see Evaluation Question 4 for further details). Preferences were specific to individual patients and should therefore be considered on a case-by-case basis by those delivering the service. ***Ongoing monitoring of potential inequalities in a national roll-out will support equitable service delivery.***

Analysis to address Evaluation Question 4 did not identify any clear inequalities related to Cytosponge. However, the sample sizes and timeframe of the pilot made this difficult. The analysis did suggest some potential areas in which inequalities might exist. These (and other areas) need further monitoring and evaluation with larger sample sizes and longer timeframes – both available within the context of a national roll-out – in order to understand whether inequalities do exist and, if so, how they might be addressed. Appropriate monitoring and evaluation of these areas will require resourcing at an appropriate level.

Clinician confidence should be addressed through the development and delivery of an education programme.

Roll-out should also be supported by resources to improve clinician confidence in the Cytosponge test results. This could be achieved through an education programme being developed and rolled-out in primary, secondary and community care. For instance, the referral process should be developed, streamlined, and communicated across the whole patient pathway. GPs require the necessary knowledge and education on Cytosponge, for instance, how to identify eligible patients, how to interpret the results, and how to manage the patients when they return to primary care.

Clear roles and support services should be established and communicated across all stakeholders.

The resources available for support and roles need to be established and clarified. For instance, peer-to-peer links between established and new sites was suggested to be a good idea moving forward. Also, when thinking back to the challenges identified with contracting, it would be helpful for clinical teams to know who would be the most helpful within their trust to support them through the contracting process (i.e., introduced to a named individual in the procurement team). Furthermore, clarification of key stakeholder roles is also needed to understand how, for instance, the Cancer Alliances could support the service going forward.

Scalability model can be used by trusts to estimate resource allocation for service delivery to support their local implementation plans.

To determine service scalability, a scalability model has been developed to support decision-making around the allocation of resources for a national level roll-out. This is an additional tool which has been developed using inputs from qualitative data collected during site-level interviews and quantitative data from the Trusts’ monthly management data.

By selecting the expected numbers of Cytosponge eligible patients waiting for an endoscopy, this interactive Excel model will display the range of FTE staff (i.e., nurses, consultants) and treatment rooms required to run the service, with the underpinning equations using the following fields:

- Trust-expected endoscopy demands.
- Proportion of patients that did not accept the Cytosponge.
- Number of incomplete and/or repeat Cytosponge procedures.
- Time spent per Cytosponge procedure and follow up activities (e.g., reviewing results and providing these to patients).
- Time spent on patient-related administrative tasks (e.g., collecting patient information) outside of the treatment room.

This universal model allows any NHS Trust to better understand the resources required in terms of nurse hours, consultant hours, room time and time for administrative tasks to scale or establish a Cytosponge service based on their trust requirements.

The budget impact models show that the initial value of the resources required for a national roll-out is between ~£1 million and ~£12 million.

The results of the BIM (see Evaluation Question 6) were used to generate a proxy estimate of the initial value of the resources required for a national roll-out of Cytosponge in England. The BIM is based on the direct variable costs of medical care and does not explicitly account for costs such as overheads, or initial outlay costs (e.g., education initiatives prior to commencement).

As the BIM results are disaggregated by phase (i.e., diagnostic pathway, and post diagnostic pathway) and by year, the aim was to evaluate the costs in year 1, in the 'world with Cytosponge' (WWC) for the proportion of patients assigned to the Cytosponge programme. This provides an estimate of the financial requirements in the first-year post launch in terms of the resources accounted for in the BIM (acquisition costs of diagnostic tests, adverse event costs, outpatient appointments etc.).

The BIM is based on an incident eligible population of 15,121 in year 1. Assuming the initial share of the population assigned to Cytosponge in year 1 is 10%, the spend during the diagnostic pathway for those assigned to the Cytosponge programme is £1,321,426. Assuming an initial share of 90%, the spend is £11,892,838.

Of note, given the budget impact results, it is likely that the cost of investment can be 'covered' by some of the budget that would otherwise be dedicated to endoscopy provision for the same number(s) of patients in a 'world without Cytosponge'.

SECTION 4: CONCLUSION

This real-world evaluation of Cytosponge as a triage tool for patients with low-risk reflux symptoms on a routine referral in secondary care shows that it is a medically effective, cost-effective and cost-saving test that would be acceptable for most patients.

Cytosponge can effectively triage patients in this cohort to remove 78% from the endoscopy waiting list (of patients who completed a Cytosponge test) and fast track those at higher risk of BO. This is a cost-effective test that has high levels of clinical and patient acceptability, and can feasibly be integrated into the existing diagnostic pathway. The effectiveness of Cytosponge in reducing endoscopy demand increased over time, and variations in how the clinical pathway were followed only had a small impact on the effectiveness of Cytosponge in reducing endoscopy demand. By discharging patients from the endoscopy waiting list following a Cytosponge test, implementing Cytosponge as a triage tool in secondary care for patients with low-risk reflux symptoms could significantly reduce endoscopy demand (Impact Evaluation and MI data).

Analysis of the diagnostic experience and outcomes of Cytosponge patients drawn from the Impact Evaluation workstream suggested that patients were being appropriately prioritised based on their test results. Specifically, patients with positive test results were more likely to be referred for an endoscopy following a Cytosponge test, and no BO diagnoses were reported amongst those who received negative Cytosponge results. However, Cytosponge appeared to lengthen the time for patients to reach the end of their diagnostic pathway. In particular, this was the case for those receiving a non-urgent endoscopy referral following their Cytosponge test. However, patients who received a Cytosponge test waited similar times to receive a BO diagnosis compared to counterfactual patients. Patients with an urgent onward endoscopy referral received their BO diagnosis or confirmed test result twice as fast as those with a routine endoscopy as a subsequent action. By reducing endoscopy demand, there is potential for other patients on the waiting list with urgent referrals to be seen more quickly.

There is compelling evidence of a positive patient experience of the Cytosponge test from analysis of the patient experience survey and subsequent 1:1 patient interview. This relates to access to services, understanding of the procedure, the timeliness and understanding of Cytosponge results and next steps, as well as clinician confidence delivering the Cytosponge service. Experience of pain during the Cytosponge test was reported to be low, although most patients experienced some mild discomfort either during or following the test, as expected, and outlined in the patient leaflet.

Analysis of patient inequalities drawn from the Impact Evaluation workstream showed no clear evidence of inequalities based on deprivation level, age or ethnicity. Some potential inequalities were found in relation to access to a diagnosis for men, based on similar proportions of test results and subsequent actions across sexes despite men being at higher risk of BO and other reflux-related disorders than women, but these require further investigation. However, the analysis was based on small sample sizes over the short pilot timeframe. There was also some evidence that Cytosponge might not be the most appropriate test for younger patients, given atypia and TFF3 are less common underlying causes for reflux in this group. As a result, younger patients might wait longer for an onward endoscopy and resulting diagnosis therefore future roll-outs should consider the most appropriate age groups for this test. It will be important to continue to monitor whether future service provision is meeting needs across different patient groups and delivering strong outcomes for all. Further monitoring and evaluation and additional quantification of the role of health inequalities in the Cytosponge programme, using larger samples of patients over longer timeframes, is needed to draw more robust conclusions.

Analysis of the barriers to and enablers of the Cytosponge programme in the Process Evaluation highlighted several key recommendations for a national roll-out, largely pertaining to the provision of administrative support, dedicated spaces to provide Cytosponge services and additional guidance for site set up. Investment to implement these recommendations would be required.

The results of the Health Economics Evaluation analysis demonstrate the Cytosponge programme is both a cost-effective and budget saving intervention relative to the standard of care when used as a triage tool in secondary care. The cost-effectiveness analysis demonstrates that the Cytosponge programme results in a per-patient cost-saving of £421.57 and a very slight decrease in QALYs of 0.0041. This difference in QALYs between the Cytosponge and endoscopy-only programme is minimal, and equivalent to a difference of 1.5 days, highlighting the extremely small nature of this decrease over a lifetime.

Analysis from the Health Economics evaluation also shows that, based on an eligible patient population of 15,121 in year 1, an initial spend of between £1,321,426 and £11,892,838 would be needed in the first-year post launch, based on 10% and 90% of eligible patients being assigned to Cytosponge respectively. Analysis also showed that the overall five-year net budget impact of introducing Cytosponge is a budget saving of between ~£10 million and ~£33 million, also based on 10% and 90% of eligible patients being assigned to Cytosponge respectively. These differences between costs and savings suggest that initial costs would be largely offset by savings.

Overall, the evaluation evidence shows that the Cytosponge pilot programme provided a safe, medically effective, cost-effective and cost-saving test that would be acceptable for almost all patients in this use case. Whilst Cytosponge could be useful across NHS trusts, in particular those with long endoscopy waiting lists and times could usefully consider using Cytosponge as a way to help address this particular issue.

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APPENDIX A: Analysis of management return data (February 2021 – April 2022)

Trust/site	Submission start	Offered	Accepted	Carried out	Referrals for Endoscopy	Barratt's diagnosed
Barking, Havering and Redbridge (BHRUT)	Mar-21	57	53	57	17	-
Bedfordshire Hospital Trust (Bedford)	Mar-21	73	72	66	37	3
Cambridge University Hospitals	Apr-21	174	173	149	42	-
Countess of Chester Hospital	Sep-21	206	165	166	54	-
Croydon Health Services NHS Trust	Aug-21	34	32	27	5	1
Cumberland Infirmary	Sep-21	47	47	40	26	2
Gloucestershire Hospital Trust	Aug-21	94	81	65	8	4
Harrogate District Trust	Jun-21	96	91	88	17	3
Kettering General Hospital	Nov-21	22	21	21	6	-
Lister Hospital	Mar-21	357	356	319	71	31
Pennine Acute Hospitals (Royal Oldham)	Jan-22	24	21	16	3	2
Queens Medical Centre (Nottingham)	Jun-21	168	159	84	15	2
Royal Hospital Exeter	Nov-21	12	12	7	1	-
Royal United Hospital (Bath)	Jun-21	94	81	65	11	1
Salford Royal Hospital (Manchester)	Mar-21	198	198	170	11	9
Shrewsbury and Telford	Sep-21	221	210	175	25	-
St Helen's Hospital	Jun-21	142	121	98	19	1
University Hospitals of Leicester	Jul-21	12	11	7	-	-
University Hospital of North Midlands (Stoke)	Jun-21	89	89	76	14	1
University Hospitals Plymouth	Jun-21	81	81	70	2	-
West Suffolk Hospital	Aug-21	47	43	41	14	1
Wigan, Wrightington and Leigh Trust	Apr-21	106	106	84	12	9
William Harvey Hospital (Kent)	Jul-21	521	460	279	66	10

Total	**2,875**	**2,683**	**2,170**	**476**	**80**
		% of offered	% of accepted	% of carried out	% of carried out
Rate		**93%**	**81%**	**22%**	**4%**

APPENDIX B: Analysis of Cyted data (February 2021 – March 2022)

Site	No. Cytosponges processed by Cyted	Adequate		Atypia = Yes (requiring 2WW endoscopy)		TFF3 positive (requiring routine endoscopy)		TFF3 Equivocal or N/A	
Barking, Havering and Redbridge (BHRUT)	28	27	96%		0%	2	7%	2	7%
Bedfordshire Hospital Trust (Bedford)	67	59	88%	1	1%		0%	6	9%
Calderdale & Huddersfield (Huddersfield)	7	7	100%	1	14%	3	43%		0%
Cambridge University Hospitals	115	115	100%	1	1%	5	4%	12	10%
Countess of Chester Hospital	129	129	100%	2	2%	5	4%	14	11%
Croydon Health Services NHS Trust	41	41	100%		0%	1	2%	7	17%
Cumberland Infirmary	69	69	100%		0%	7	10%	6	9%
Gloucestershire Hospital Trust	64	64	100%	1	2%	5	8%	5	8%
Guy's and St Thomas NHSFT	2	2	100%		0%	1	50%		0%
Harrogate District Trust	78	78	100%	1	1%	7	9%	8	10%
Hull University Teaching Hospital	3	3	100%		0%	1	33%		0%
Kettering General Hospital	22	22	100%	1	5%		0%	6	27%
Lancashire Teaching Hospitals NHSFT	39	39	100%		0%	5	13%	8	21%
Lister Hospital	276	263	95%	2	1%	30	11%	16	6%
Pennine Acute Hospitals (Royal Oldham)	7	7	100%		0%	1	14%		0%
Queens Medical Centre (Nottingham)	82	82	100%		0%	9	11%	6	7%
Royal Hospital Exeter	14	14	100%		0%	3	21%	2	14%
Royal United Hospital (Bath)	64	64	100%	2	3%		0%	8	13%
Salford Royal Hospital (Manchester)	128	125	98%	3	2%	8	6%	10	8%
Shrewsbury and Telford	96	96	100%	3	3%	7	7%	5	5%
St Helen's Hospital	86	85	99%	1	1%	7	8%	4	5%
University Hospitals of Leicester	8	8	100%		0%	1	13%		0%
University Hospital of North Midlands (Stoke)	39	39	100%	1	3%	4	10%	2	5%
University Hospitals Plymouth	55	55	100%	1	2%	2	4%	5	9%
University Hospitals Dorset	11	11	100%	1	9%	1	9%		0%
West Suffolk Hospital	26	26	100%		0%	3	12%	5	19%
Wigan, Wrightington and Leigh Trust	55	52	95%		0%	5	9%	4	7%
William Harvey Hospital (Kent)	231	228	99%	1	0%	14	6%	31	13%
York District Foundation Trust	4	4	100%		0%		0%		0%
Grand Total	**1,846**	**1,814**	**98%**	**23**	**1%**	**137**	**7%**	**172**	**9%**

APPENDIX C: Summary table of patient demographics from survey

Overall Demographics	N	%
Age		
16-24*	4	1%
25-34	29	9%
25-44	41	13%
45-54	56	17%
55-64	100	31%
65-74	72	22%
75-84	22	7%
Sex (at birth)		
Male	133	38%
Female	217	62%
Ethnicity		
White	335	98%
Non-White	8	2%
Previous Endoscopy		
Yes	122	35%
No	219	64%

** Patients under 25 years of age were excluded from data analysis due to suppression levels.*

APPENDIX D: Management data – breakdown of onward referral to endoscopy rate following Cytosponge result by site (February 2021 – April 2022)

Trust	Number of Cytosponges completed	Number of confirmatory endoscopies performed	Onward referral rate (%)
Barking, Havering and Redbridge (BHRUT)	57	17	29.8
Bedfordshire Hospital Trust (Bedford)	66	37	56.1
Cambridge University Hospitals	149	42	28.2
Countess of Chester Hospital	166	54	32.5
Croydon Health Services NHS Trust	27	5	18.5
Cumberland Infirmary	40	26	65
Gloucestershire Hospital Trust	65	8	12.3
Harrogate District Trust	88	17	19.3
Kettering General Hospital	21	6	28.6
Lister Hospital	319	71	22.3
Pennine Acute Hospitals (Royal Oldham)	16	3	18.8
Queens Medical Centre (Nottingham)	84	15	17.9
Royal Hospital Exeter	7	1	14.3
Royal United Hospital (Bath)	65	11	16.9
Salford Royal Hospital (Manchester)	170	11	6.5
Shrewsbury and Telford	175	25	14.3
St Helens Hospital	98	19	19.4
University Hospitals of Leicester	7	0	0
University Hospitals of North Midlands (Stoke)	76	14	18.4
University Hospitals Plymouth	70	2	2.9
West Suffolk Hospital	41	14	34.1
Wigan, Wrightington and Leigh Trust	84	12	14.3
William Harvey Hospital (Kent)	279	66	23.7
Total	**2170**	**476**	**22.3***

**Calculated as the average (mean) of onward referral rate of all sites*