ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

Cytosponge for the Detection of Patients with Barrett Oesophagus

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Summary of Key Points

- Barrett oesophagus (BO) is an underdiagnosed condition associated with chronic gastro-oesophageal reflux disease (GORD). It is a precursor of oesophageal adenocarcinoma (OAC), which presents a poor prognosis.
- Oesophagogastroduodenoscopy (OGD) is the gold standard for diagnosing BO. Use is limited by cost, invasive nature and need for sedation.
- Cytosponge (Medtronic) is a single use 'sponge on a string' device that can be used in primary care or outpatient clinics to collect cells lining the oesophagus. The cell sample can be analysed by various biomarker candidates including trefoil factor 3 (TFF3), which is a histopathological hallmark of BO.
- Based on the relatively mature evidence base for the TFF3 biomarker and the use of Cytosponge as an initial diagnostic test, this brief focused on Cytosponge-TFF3 for the detection of BO.
- Overall, Cytosponge was found to be generally safe and effective.
    - The rate of reported serious adverse events, including sponge detachment and pharyngeal bleeding, was low.
    - Cytosponge was significantly more acceptable to patients with upper GI conditions than endoscopy, particularly endoscopy performed without sedation ($p<0.001$).
    - A pooled analysis reported good diagnostic accuracy (81% sensitivity and 91% specificity) in the detection of BO by Cytosponge compared to endoscopy, with most of the studies utilising TFF3 as a biomarker of BO.
    - In patients on medication for acid reflux, the use of Cytosponge-TFF3 followed by confirmatory endoscopy improved the diagnostic yield of BO by around 10-fold compared to usual care.
    - Cytosponge has the potential to benefit the healthcare system by reducing the number of staff required, enabling targeted endoscopies and reducing transmission risk of infectious diseases.
- The clinical utility of Cytosponge in terms of patient health outcomes, such as OAC incidence, remains to be investigated.
- Reflecting real-world clinical utilisation, it was reported that the use of Cytosponge-TFF3 as a triage test with confirmatory endoscopy was cost-effective over standard care, with an incremental cost-effectiveness ratio of £5,500 per quality-adjusted life year gained.
- Cytosponge-TFF3 testing was estimated to cost S$449.
- Key implementation considerations include staff training, potential need for investment in digital pathology technologies, and clinical oversight of artificial intelligence software with future developments of the technology.
- Of note, the National Health Service (NHS) Scotland has adopted Cytosponge as a triage test for the detection of patients with BO.
- Despite a favourable profile, Cytosponge has limited utility in the local context, mainly due to low BO prevalence in symptomatic patients with GORD and to different care pathways.

I. Background

Barrett oesophagus (BO) is the only known precursor to oesophageal adenocarcinoma (OAC), a highly lethal cancer.[1] BO is associated with chronic gastro-oesophageal reflux disease (GORD), where prolonged exposure of stomach acid to the oesophagus squamous epithelium leads to persistent inflammation and a columnar metaplasia reaction, with subsequent development of an intestinal-type phenotype.[2] Most patients with BO exhibit symptoms of GORD such as heartburn and acid regurgitation. Less common symptoms include dysphagia and a globus sensation. In rare cases, patients may be asymptomatic.[2]

Globally, BO is found in 1.3% to 1.6% of the general population.[2] In patients with GORD symptoms, the pooled global prevalence of histologically confirmed and endoscopically suspected BO were found to be 7.2% and 12%, respectively.[3] Notably, the prevalence of BO and GORD was found to be lower in Asian countries than in Western countries, although rising prevalence in Asia is anticipated.[3-6] Locally, the prevalence of BO was reported to be 1.7% in a symptomatic GORD population.[4] Although most patients will not develop a malignancy, BO may progress into OAC if left untreated. Locally, OAC presents a poor prognosis. It is the 10th most common cause of cancer-related death in males and has a five-year survival rate after surgical resection of 5% to 30%.[7] Despite the poor prognosis, early detection in patients with precancerous BO can improve survival outcome with a five-year disease-free survival rate of around 80% after surgery.[7]

Oesophagogastroduodenoscopy (OGD), also known as upper GI endoscopy, is the gold standard for BO diagnosis. However, use is limited by cost, invasive nature and the need for patient sedation. Currently, only around 20% of patients with BO are diagnosed with OAC, with most cases diagnosed de novo without the opportunity to prevent progression.[8] As such, there remains a clinical unmet need for a minimally invasive, readily accessible and low cost method to detect patients with early stage BO who may benefit from treatment to prevent escalation to OAC.[9]

II. Technology

Cytosponge (Medtronic) is a single use 'sponge on a string' device that collects cells from the lining of the oesophagus. It consists of a spherical sponge enclosed in a capsule attached to a string (Figure 1). When the capsule is swallowed, it dissolves in the stomach and releases the self-expanding sponge. After seven and a half minutes, the string is gently pulled to retrieve the sponge. The sponge collects cells lining the oesophagus as it is retracted. The collected cells are sent to a laboratory for further analysis. The sample analysis can be performed with various biomarkers, including immunohistochemical

Figure 1. Illustration of the Cytosponge device. Image adapted from https://refluxuk.com/symptoms-and-diagnosis/diagnostic-tests/cytosponge/

staining with trefoil factor 3 (TFF3) that detects intestinal metaplasia (IM), which is a histological hallmark of BO.[8]

Cytosponge provides a minimally invasive and low-cost alternative to endoscopy that can potentially improve access for patients with chronic GORD to diagnostic services, in settings such as primary care or outpatient clinics. This may enable early diagnosis of BO before it progresses to OAC. Another proposed use for Cytosponge is as a surveillance tool, to monitor patients previously diagnosed with BO.[10] Of note, the test is unable to determine the length of a Barrett segment or other structural abnormalities which would require visual examination with an endoscopy.[11]

III. Regulatory and Subsidy Status

Cytosponge was approved by the US Food and Drug Administration (FDA) in 2014 and was also Conformité Européenne (CE) marked.

In the UK, the rollout of Cytosponge has been funded by the Scottish Government as an alternative investigative modality to upper gastrointestinal (GI) endoscopy for (i) patients with GORD symptoms, who are referred for upper GI endoscopy with concern of BO, pre- or early OAC, or (ii) patients with known BO who are at risk of OAC with progressive symptoms and/or had significant delay in their upper GI endoscopy.[12]

IV. Stage of Development in Singapore

☒	Yet to emerge	☐	Established
☐	Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☐	Established *but* modification in indication or technique
☐	Nearly established	☐	Established *but* should consider for reassessment (due to perceived no/low value)

V. Treatment Pathway

International guidelines and consensus groups, including the American College of Gastroenterology (ACG), British Society of Gastroenterology (BSG), and the Asia-Pacific consensus, identify endoscopy as the gold standard for diagnosis of BO.[1,13-15] Diagnosis is based on visual evidence of columnar-lined epithelium along with histological confirmation from oesophageal biopsies.[1,13,15]

While local practice for the diagnosis of BO is largely consistent with international guidelines, there are some differences. For example, unlike the ACG guidelines, the Asia-Pacific consensus paper recommended that the presence of IM is not required for the diagnosis of BO due to sampling bias that may confound diagnosis.[15] Furthermore, local clinical expert opined that in patients with GORD symptoms, endoscopy is also recommended to rule out other associated upper GI conditions such as gastric cancer, peptic ulcer disease and

Helicobacter pylori associated chronic gastritis due to its higher local prevalence compared to Western countries (Personal communication: Senior Consultant from Changi General Hospital, 2 February 2023).

Following a diagnosis of BO, both ACG and BSG generally recommend endoscopic surveillance to detect for early cancer despite a lack of high-quality supporting evidence.[1,13] The surveillance interval is contingent upon the presence of abnormal cells (e.g., IM) and the length of Barrett segment (e.g., endoscopy every three years for Barrett segment ≥3cm).[1,13] On the other hand, the Asia-Pacific consensus paper indicated no clear benefit in the endoscopic surveillance of BO in the absence of dysplasia while it may be more relevant in those with low-grade dysplasia.[15]

VI. Summary of Evidence

The assessment was conducted based on the Population, Intervention, Comparator and Outcome (PICO) criteria presented in Table 1. Literature searches were conducted in health technology assessment (HTA) databases, Cochrane library, PubMed and Embase. Given the relatively mature evidence base for the TFF3 biomarker and the use of Cytosponge as an initial diagnostic tool, this brief focused on Cytosponge coupled with TFF3 for the detection of BO.[16] The key evidence base consists of two recent HTA reports from the National Institute for Health and Care Excellence (NICE)[17] and Healthcare Improvement Scotland (HIS)[18], as well as a diagnostic accuracy study[19] and an economic evaluation.[20] Some overlap was noted in the studies reviewed by NICE and HIS, including two systematic reviews (SRs)[21,22] and one randomised controlled trial (RCT)[8].

Eight other studies[23-30] served as supplementary evidence including: two horizon scanning reports from the Canadian Agency for Drugs and Technologies in Health (CADTH)[23] and the Agency for Healthcare Research and Quality (AHRQ)[25]; five studies[26-30] that investigated the use of biomarker candidates other than TFF3 for analysis of Cytosponge samples; and a study[24] that evaluated the cost-effectiveness of Cytosponge as a surveillance tool. The study design and characteristics of the key and supplementary evidence sources are presented in Tables A1 and A2 (Appendix A).

Table 1: Summary of PICO criteria

Population	Patients with GORD symptoms who are suspected of BO
Intervention	Cytosponge
Comparator	Endoscopic confirmation of BO
Outcome	Safety, clinical and cost-effectiveness
Abbreviations: BO, Barrett oesophagus; GORD, gastro-oesophageal reflux disease.	

Safety

Key safety and acceptability findings for Cytosponge comes from a SR[22] included in both the NICE and HIS reports. Overall, these reports found Cytosponge to be generally safe with a low rate of serious adverse events (SAEs).[17,18] To assess safety, the SR pooled data across six studies conducted in Australia, UK and US, accounting for 2,672 procedures. Over 96% of patients successfully swallowed the Cytosponge. Two device-related SAEs were recorded: detachment of the sponge in one patient and pharyngeal bleeding after Cytosponge

withdrawal in another patient.[17] Similarly, a low rate of SAE was reported in the BEST3 RCT, with one (0.06%) sponge detachment reported in 1,654 individuals.[8,17] Among this same cohort, adverse events (AEs) were reported in 142 (9%) individuals, including sore throat in 63 (4%) individuals.[8,17]

The same SR also reported that Cytosponge had a satisfactory overall acceptability across 2,289 patients with GORD, BO or eosinophilic oesophagitis.[17,18] Using a visual analogue scale, Cytosponge was found to be more acceptable compared to endoscopy performed without sedation ($p<0.001$), but less acceptable than endoscopy with sedation ($p<0.001$; Figure B1 in Appendix B).[17,18] Similarly, CADTH concluded that the Cytosponge procedure was less onerous for patients compared to endoscopy (Table B1 in Appendix B).[23] Likewise, early findings from a cross-sectional study abstract (n=197) reviewed by NICE reported that 65% of people preferred Cytosponge over endoscopy.[17]

Effectiveness

Accuracy

The diagnostic accuracy of Cytosponge for the detection of BO was largely summarised in another SR[21] reviewed by NICE and HIS.[17,18] Of the six pooled studies included in the SR that reported on diagnostic accuracy of Cytosponge, the majority utilised TFF3 as a biomarker of BO to stain the exfoliated cells collected by Cytosponge.[21] Using endoscopy as the reference standard, the pooled sensitivity and specificity of Cytosponge for the detection of BO were 81% (range, 67.5% to 100%) and 91% (range, 67.3% to 100%), respectively (Table 2).[17,18] Among the six studies, four studies reported the diagnostic accuracy of Cytosponge-TFF3 with sensitivity and specificity ranging from 78% to 90% and 92.4% to 94%, respectively.[21]

Of note, the HIS report observed that sensitivity of BO detection improved when longer sections of tissue were present (Table 2).[18] Similar findings by Shaheen et al. (2022)[19] also reported improved sensitivity of Cytosponge-TFF3 to detect BO tissues (from 76% to 86%) when a cut-off of ≥3cm was used.

In addition, findings from the BEST3 trial reported that 131 out of 221 people with a positive Cytosponge-TFF3 result were diagnosed with BO or stage I oesophago-gastric cancer upon a confirmatory endoscopy, indicating a positive predictive value (PPV) of 59%.[17] The PPV is related to the prevalence of BO, which was assumed to be modest (4%) in the study population.[8]

Table 2: Diagnostic accuracy of Cytosponge for the detection of BO from the HIS report

Study	N	Population	Biomarker	Sensitivity	Specificity
Cohort study (UK; BEST1)	501	Patients on acid suppressant medication for ≥3 months in the past 5 years	TFF3	73.3% (patches ≥1cm) 90.0% (patches ≥2cm)	93.8% (patches ≥1cm) 93.5% (patches ≥2cm)
Case-control (UK; BEST2)	1,042	Patients with BO (cases) and dyspepsia (control)	TFF3	79.9%	92.4%
Case-control (UK)	59	Patients with known dysplastic (cases) and non-dysplastic BO (controls)	Cancer hotspot panel	71.4%	90.3%

RCT (US)	40	Patients with and without BO	VAV3 and ZNF682	100%	100%
Case-control (UK)	146	Patients with BO and healthy controls	TFF3	78%	94%
Cross-sectional (UK)*	73	Patients with known BO	TFF3	91.5%	NR
Case-control (UK)	97	Patients with BO and healthy controls	Mcm2	67.5% 76% (patches ≥3cm)	67.3%
Pooled accuracy	**1,957**	**—**	**—**	**81%**	**91%**

* Study not included in the pooled data owing to missing specificity data.

Abbreviations: BO, Barrett oesophagus, Mcm2, Minichromosome Maintenance Complex Component 2; NR, not reported; RCT, randomised controlled trial; TFF3, trefoil factor 3; VAV3; Vav Guanine Nucleotide Exchange Factor 3; ZNF682, Zinc Finger Protein 682.

Note: Table adapted from the HIS report[18].

Aside from TFF3, other biomarkers such as zinc finger proteins, microRNAs or multigene biomarker panels have been investigated for the detection of BO from Cytosponge samples (see Tables C1 to C3 in Appendix C).[26-30] However, these biomarker candidates remain investigational and further validation is required to assess their clinical applicability.[26-30] Notably, several studies[27,29,30] have indicated that risk stratification of patients who tested positive for Cytosponge-TFF3 could be augmented by screening for additional biomarkers such as tumour protein 53 (TP53) and c-Myc mutations, which indicate the presence of high-grade dysplasia.[23]

Diagnostic yield

The diagnostic yield of Cytosponge was reported in one RCT (BEST3) included in both the NICE and HIS reports.[17,18] Overall, compared to usual care, Cytosponge-TFF3 significantly increased the number of individuals identified with BO.

BEST3 showed that Cytosponge-TFF3 offered to patients on medication for acid reflux significantly increased the diagnosis of BO by around 10-fold over a 12-month period compared to usual care in the primary care setting (adjusted relative risk, 10.6; 95% CI, 6.0 to 18.8; p<0.0001; Table 3).[8,17,18] Of note, although individuals in the Cytosponge arm were offered a choice of Cytosponge or usual care, the Cytosponge uptake rate was low (approximately 25.6%). This suggests the possibility that individuals who opted for Cytosponge may have more problematic symptoms than those who did not, although this bias was addressed by the study using an intention-to-treat analysis.[8]

Table 3: Diagnostic yield of BO with Cytosponge-TTF3 *vs.* usual care

	Usual care (n=6,834)	Cytosponge-TFF3* (n=6,388)	Absolute difference in rates per 1000 person-years (95% CI)	Overall rate ratio (95% CI)	Overall adjusted rate ratio (95% CI); p-value
Number of people diagnosed with BO	13 (<1%)	140 (2%)	—	—	—
Follow-up, person-years	6,579	6,952	—	—	—
Rate of BO, per 1000 person-years	2.0	20.2†	18.3 (14.8 to 21.8)	10.2 (5.8 to 18.1)	10.6 (6.0 to 18.8)‡; p<0.0001

* Individuals in the Cytosponge group were offered a choice of Cytosponge or usual care. The number of participants diagnosed with BO in the Cytosponge group were analysed based on the intention-to-treat population, regardless if the Cytosponge procedure was conducted.

† The rate of BO in the intervention group was calculated as the weighted average of the rate in the first 4 months of follow-up and the rate in the following months, with a weight ratio of 1.2.

‡ The overall adjusted rate ratio is a combined rate ratio of the cluster and patient-level randomisation groups, and accounts for clustering.

Abbreviations: BO, Barrett oesophagus; CI, confidence interval; TFF3, trefoil factor 3; UK, United Kingdom; US, United States.

Table adapted from Fitzgerald et al. (2020)[8].

Clinical Utility

No studies reported on the clinical utility of Cytosponge in terms of patient health outcomes. However, there were some indications that the Cytosponge-TFF3 procedure may impact treatment plans based on findings from BEST3. In the intervention group, eight patients were diagnosed with BO or stage I cancer following Cytosponge-TFF3 testing and were suitable for curative therapy. In contrast, no patients were diagnosed with early-stage disease in the usual care group, with late-stage cancer found in five patients who were treated with palliative or best supportive care.[8] This suggests the potential of Cytosponge to guide early therapeutic interventions before disease progression to achieve better health outcomes, although further validation is required.

Healthcare system benefits

Cytosponge may confer benefits at the healthcare system level. As a triage test, it is expected to replace endoscopy as a first-line diagnostic tool. This may lead to better healthcare resource utilisation, as Cytosponge can be offered in primary care, potentially freeing up healthcare resources in tertiary care and specialty centres and allowing targeted endoscopies to be performed. Furthermore, Cytosponge can be administered by a single staff member in contrast to endoscopy, which is an invasive procedure requiring sedation and involvement of multiple healthcare professionals. Notably, the National Health Service (NHS) reported that the use of Cytosponge as a triage tool has diverted a significant number of patients from the national endoscopy waitlist, addressing the mounting backlog of upper GI endoscopies in England.[31]

In addition, Cytosponge is less aerosol-generating compared to endoscopy and can reduce risk of infectious disease transmission to healthcare workers.[32]

Cost-effectiveness

Based on three economic evaluations included in two studies,[18,20] Cytosponge was found to be cost-effective for the detection of BO compared to usual care (symptomatic management and physician-referred endoscopy) or no screening (natural history or symptomatic management only). In a cost-utility analysis (CUA)[20] reflecting the potential real-world clinical use of Cytosponge as a triage test, a diagnostic strategy of Cytosponge-TFF3 with subsequent confirmatory endoscopy was found to be cost-effective over usual care with an incremental cost-effectiveness ratio (ICER) of £5,500 per quality-adjusted life year (QALY) gained in patients aged 50 years and above on medication for acid reflux (Table 4). At a willingness-to-

pay threshold of £20,000 per QALY, there was a 97% probability that Cytosponge-TFF3 remained cost-effective compared to usual care.[20]

The cost-effectiveness of Cytosponge over usual care for the detection of BO was further substantiated by findings from two microsimulation modelling studies in males with GORD symptoms (Table 4).[18] When compared to no screening, the UK model reported that a diagnostic strategy with endoscopy screening (ICER, US$22,167 per QALY gained) was dominated by Cytosponge-first screening (ICER, US$15,724 per QALY gained), where screening with Cytosponge was less costly and more effective than endoscopy.[18] Similarly, the US model reported an ICER varying from US$143,041 to US$330,361 per QALY gained with endoscopy screening compared to Cytosponge-TFF3-first screening, with the wide ICER range owing to the use of two independent models to model the natural history of OAC.[18,33] Based on this, the study authors concluded that a Cytosponge-first strategy may be a cost-effective method to screen for BO while endoscopic screening was a non-cost-effective approach.[33]

Table 4: Cost-effectiveness of Cytosponge for the detection of BO

Study	Population	Intervention	Comparator	ICER
Cost-utility analysis; Swart et al. (2021)[20]	Patients aged ≥50 years old on medication for acid reflux	Cytosponge-TFF3 with confirmatory endoscopy and treatment	Usual care*	£5,500 per QALY gained
Microsimulation modelling (UK); HIS[18]	50-year-old men with GORD symptoms	Cytosponge-first screening, followed by confirmatory endoscopy	No screening†	US$15,724 per QALY gained
		Endoscopy	No screening†	US$22,167 per QALY gained
Microsimulation modelling (US); HIS[18]	60-year-old men with GORD symptoms	Cytosponge-TFF3-first screening, followed by confirmatory endoscopy	No screening†	US$28,791 to US$33,307 per QALY gained
		Endoscopy	Cytosponge-TFF3-first screening, followed by confirmatory endoscopy	US$143,041 to US$330,361 per QALY gained

* Includes treatment of heartburn-predominant symptoms and referral for endoscopy as deemed necessary by the primary care physician.

† Refers to natural history of disease or symptomatic management only.

Abbreviations: BO, Barrett oesophagus; GORD, gastro-oesophageal reflux disease; HIS, Healthcare Improvement Scotland; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year; TFF3, trefoil factor 3; UK, United Kingdom; US, United States.

Besides the detection of BO, Cytosponge was also reported to serve as a cost-effective surveillance tool for patients previously diagnosed with BO following radiofrequency ablation compared to other strategies (see Table C4 in Appendix C).[24]

Ongoing trials

Six ongoing trials were identified from the ScanMedicine database (NIHR Innovation Observatory; Table 5). Three of the studies are investigating the feasibility, acceptability and utility of Cytosponge to identify or monitor BO. The others are assessing the use of Cytosponge for other indications, including eosinophilic esophagitis, oesophageal squamous cell carcinoma and gastric intestinal metaplasia. The NIHR Cambridge Biomedical Research

Centre has also reported that trials are underway to evaluate the role of Cytosponge to monitor patients with BO.[10]

Table 5: Ongoing clinical trials

Study (Trial ID)	Estimated enrolment	Brief description	Estimated completion date
DELTA (ISRCTN91655550)	3,000	An observational study to assess the feasibility and practical implementation steps of introducing Cytosponge-TFF3 as a triage test for endoscopy to identify BO, early cancer and other oesophageal conditions.	June 2023
Comparison of Histology From a Mesh Sponge and Traditional Esophageal Biopsies in Children and Adolescents With EoE (NCT05342168)	30	A cross-sectional study in paediatric subjects comparing histologic findings on oesophageal biopsies obtained during upper GI endoscopies to histologic findings on tissue samples obtained through the use of the Cytosponge in a group of paediatric patients with a diagnosis of EoE.	September 2023
REACT (NCT03366012)	100	A single-arm study to evaluate the acceptability of a new non-invasive screening device to test for BO.	December 2023
PROBAN (NCT04155242)	147	A prospective study to assess the utility of a panel of molecular biomarkers for predicting the risk of relapse of BO after endoscopic treatment of early oesophageal neoplasia with radiofrequency ablation.	December 2024
Esophageal Squamous Cell Cancer Surveillance With Cytosponge (NCT04192695)	50	A prospective cohort study to identify molecular abnormalities at each developmental stage of oesophageal squamous cell carcinoma (low-grade intraepithelial neoplasia, high-grade intraepithelial neoplasia, and early squamous cell carcinoma) in order to establish new molecular biomarkers with potential for early detection and surveillance of the disease using the minimally invasive Cytosponge cell collection device	November 2024
CyGIM (NCT05657080)	226	A case-control study to compare the non-endoscopic test (Cytosponge-TFF3) to standard endoscopy to diagnose gastric intestinal metaplasia, a precursor lesion for gastric cancer.	October 2023
Abbreviations: BO, Barrett oesophagus; EoE, eosinophilic esophagitis; GI, gastrointestinal; TFF3, trefoil factor 3.			

Summary

Overall, Cytosponge was found to be safe, clinically- and likely cost-effective. The device had a low rate of SAEs including sponge detachment and pharyngeal bleeding, while being less onerous and more acceptable for patients compared to endoscopy without sedation. Pooled analysis indicated a sensitivity of 81% and specificity of 91% for Cytosponge in the detection of BO compared to endoscopy. Sensitivity improved with longer section of BO tissues. Moreover, for patients on medication for acid reflux, the use of Cytosponge-TFF3 followed by confirmatory endoscopy improved the diagnostic yield of BO by around 10-fold compared to usual care in the primary care setting. This has the potential to allow earlier therapeutic intervention before disease progression and reduce the incidence of OAC, although further validation is required. In addition, Cytosponge may bring potential benefit to the healthcare system by reducing the number of staff required for testing, enabling targeted endoscopies to optimise resource use, and lower risk of infectious disease transmission. In terms of cost-effectiveness, Cytosponge was reported to be cost-effective over usual care. Reflecting its potential real-world clinical use, Cytosponge yielded an ICER of £5,500 per QALY gained when used as a triage test with follow-up endoscopy to detect BO, compared to usual care.

Findings described in this brief should be interpreted in view of potential bias. Most studies were conducted by the team that developed the technology, and assessed by NICE to be of low quality.[18] Further studies are required to validate the clinical utility of Cytosponge-TFF3 testing on long term patient outcomes, such as the incidence of OAC.

VII. Estimated Costs

According to NICE, Cytosponge costs £280 (S$449)[a] before tax, inclusive of the device itself, the TFF3 assay and a haematoxylin and eosin stain test to ascertain the presence of gastric cells.[17] An earlier report by AHRQ estimated Cytosponge testing to cost £25 (S$40)[a] as compared with around £600 (S$962)[a] for conventional endoscopic evaluation for BO.[25]

VIII. Implementation Considerations

The adoption of the Cytosponge test may raise several key implementation considerations. These involve staff training and workload, and potential need for investment in digital pathology technologies and clinical governance of artificial intelligence (AI) software with future developments of the technology.

To enable ease of test administration, ample training would be required for primary care nurses or healthcare professionals to handle and process the sponges during and after the procedure.[17] The anticipated increased use of Cytosponge testing, together with the aim to maintain a clinically acceptable turnaround time, may subsequently require additional histopathology staff to prepare, test and interpret the Cytosponge samples.

The introduction of Cytosponge may serve to improve patient's access to endoscopy for confirmation of BO diagnosis. However, acceptability of the test may encourage uptake by patients with GORD symptoms and inadvertently increase the number of patients identified with and treated for BO. Consequently, this may increase the number of patients placed on surveillance, leading to longer wait times and costs for endoscopy.[23] In response to this potential concern, ongoing works are in development to better stratify patients who test positive for BO with Cytosponge-TFF3. As discussed in Section VI, various biomarker panels are being investigated to distinguish between high and low risk TFF3-positive cases. In the future, this may allow low-risk TFF3-positive patients to be placed on ongoing surveillance with Cytosponge, reducing the burden on endoscopy services and the risk of overtreatment.[16]

It should also be noted that in response to the well-defined staining observed with TFF3 together with the binary nature of the scoring system, AI-based tools are currently being developed to highlight abnormalities in TFF3 staining for confirmation by pathologists.[16] This implies a potential need for investment in digital pathology technologies that should be considered alongside the adoption of Cytosponge. In addition, the use of AI technologies would involve further regulatory considerations. Briefly, as outlined in the Ministry of Health (MOH) Artificial Intelligence in Healthcare Guidelines (AIHGle), it is crucial to exercise clinical governance and oversight of any AI-medical devices, such as risk assessment, performance

[a] Based on the Monetary Authority of Singapore exchange rate as of 6 January 2023: £1=S$1.6025. Figures were rounded to the nearest dollar.

tracking, assessing cybersecurity vulnerabilities, staff training and transparency in end-user communications.[34]

IX. Concurrent Developments

Similar to Cytosponge, two other technologies that provide non-endoscopic sampling of oesophageal cells were identified (Table 6). These technologies were approved by FDA and samples collected can be tested with various biomarkers.

Table 6: Similar technologies in development

Technology (Manufacturer)	Brief description	Status
EsoCheck Esophageal Cell Collection Device (Lucid Dx Labs)	EsoCheck is a cell collection device that is designed to collect cells of a targeted region of the esophagus without the need for endoscopy. The sampled cells can then be subjected to any commercially available diagnostic test. Of note, FDA has granted breakthrough device designation for EsoGuard to test esophageal samples collected using the company's EsoCheck Cell Collection Device, in patients who are at high risk for esophageal dysplasia due to chronic gastro-oesophageal reflux disease.	FDA approved
EsophaCap (PAVmed)	The EsophaCap is a non-sterile, non-endoscopic, single use oesophageal cell sampling device	
Abbreviation: FDA, US Food and Drug Administration.		

X. Additional Information

In April 2022, ACG updated their guidelines for the diagnosis and management of BO to include Cytosponge as an acceptable alternative to endoscopy, to screen for BO in patients with chronic reflux symptoms and other risk factors.[1] To add, experts consulted by NICE agreed that Cytosponge can be used as a screening or triage tool to identify individuals who require upper GI endoscopy for the diagnosis of BO.[17] Similarly, experts consulted by AHRQ commented that the convenience of Cytosponge testing may overcome the issue of underdiagnosing BO to potentially improve overall health outcomes.[25] Cytosponge is supported by the NHS Golden Jubilee's Centre for Sustainable Delivery and over 5000 Cytosponge procedures have been performed across Scotland (as of 3 November 2022).[35] In particular, NHS Lothian has established Cytosponge clinics as an alternative to upper GI endoscopy for BO surveillance.[12]

Consensus from local experts is that Cytosponge may have limited utility in the local context despite its clinical performance. Currently, local clinical practice is to always offer upper GI endoscopy to symptomatic patients with GORD owing to the inability of some patients to accurately describe their GORD symptoms and the need to rule out other associated oesophageal and gastric conditions which have a relatively higher prevalence in the local setting compared to the Western context. In addition, access to upper GI endoscopy is quick and easy for all patients in local healthcare institutions, while the local prevalence of BO is lower compared to the Western countries. Moreover, based on the Asia-Pacific consensus paper,[15] the detection of IM in the oesophagus is no longer required for the diagnosis of BO in the local context and the use of the TFF3 biomarker may potentially lead to an under-

diagnosis of BO. Also, the short segment and mild nature of BO cases in Asia warrants the need for targeted biopsies for diagnostic confirmation.

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Appendix

Appendix A: Studies identified and study design

Table A1: List of included studies

Type of study	Key evidence base	Supplementary evidence base
Health technology assessment (HTA) report	2	—
Horizon scanning report	—	2
Published studies	2	6

Note:
1. Inclusion criteria
   a. Studies that fulfil the PICO criteria listed in Table 1.
2. Exclusion criteria
   b. Studies only available in the abstract form.

Table A2: Design and characteristics of included studies

Study	Study type	Number of studies/patients	Population
Key evidence base			
NICE (2020)[17]	HTA	5 studies (2 SRs, 1 RCT and 2 cross-sectional studies)	Patients with suspected or known BO
HIS (2020)[18]	HTA	6 studies (2 SRs, 1 RCT, 1 qualitative study and 2 economic evaluations)	Patients with suspected or known BO
Shaheen et al. (2022)[19]	Diagnostic accuracy	191 patients	Patients with confirmed BO or heartburn/regurgitation for ≥ 6 months
Swart et al. (2021)[20]	Cost utility analysis	13,668 patients	Patients with heartburn-predominant symptoms and referral for endoscopy as deemed necessary by the primary care physician
Supplementary evidence base			
CADTH (2015)[23]	HS report	5 studies (including 2 economic evidence)	Patients with suspected or known BO
AHRQ (2015)[25]	HS report	4 studies (including 1 economic evidence)	Patients with suspected or known BO
Eluri et al. (2022)[24]	Cost utility analysis	234 patients	Patients with dysplastic BO after at least one round of radiofrequency ablation
Chettouh et al. (2017)[26]	Diagnostic accuracy	308 patients*	Patients with BO (cases) and normal squamous oesophageal biopsies (control)
Li et al. (2018)[28]	Diagnostic accuracy	64 patients	Patients with BO (cases) and those referred for endoscopy due to dyspepsia or reflux symptoms with BO (control)
Ross-Innes et al. (2017)[30]	Diagnostic accuracy	533 patients†	Patients with BO and intestinal metaplasia.
Katz-Summercorn et al. (2017)[27]	Diagnostic accuracy	59 patients	Patients with non-dysplastic and dysplastic BO
Pilonis et al. (2022)[29]	Diagnostic accuracy	891 patients‡	Patients older than 18 years old who were having endoscopic surveillance for BO

* Including patients in the pilot (n=30) and validation (n=278) cohorts.

† Including patients in the discovery (n=468) and validation (n=65) cohorts.

‡ Including patients in the training (n=557) and validation (n=334) cohorts.

Abbreviations: BO, Barrett oesophagus; HS, horizon scanning; HTA, health technology assessment; RCT, randomised controlled trial; SR, systematic review.

Appendix B: List of supplementary tables and figures

Table B1: Acceptability of the Cytosponge procedure as reviewed by CADTH

Study	N	Key findings
Case-control (UK; BEST2)	1,100	• More than 97% of the participants rated their Cytosponge experience as 3 or higher (mildly unpleasant or better) on a 10-point scale (0: worst imaginable experience; 5: neutral; 10: very enjoyable experience) • The rating for Cytosponge was significantly higher than that for endoscopy • Of note, patients who did not receive sedation for their endoscopy were more likely to give the Cytosponge procedure a higher score
Case-control (UK)	97	• In 43 patients with known BO and 54 healthy volunteers who received the Cytosponge test, the overall acceptability rating of the test was 4 on a 10-point scale (0: worst imaginable experience; 5: neutral; 10: very enjoyable experience) • Of the patients with known BO who had experienced endoscopy, 80% would prefer surveillance with Cytosponge than endoscopy
Abbreviations: BO, Barrett oesophagus; CADTH, Canadian Agency for Drugs and Technologies in Health; UK, United Kingdom.		

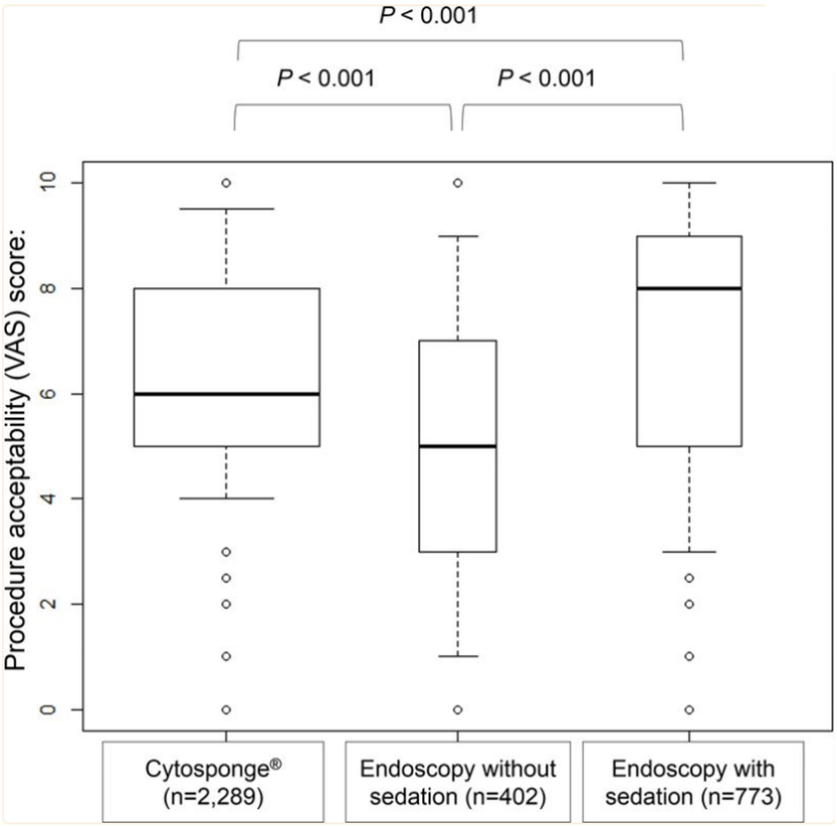

Figure B1: Acceptability of Cytosponge and endoscopy. Figure adapted from Januszewicz et al. (2019)[22].

Appendix C: Other supporting information pertaining to the Cytosponge test

Table C1: Diagnostic accuracy of biomarker candidates for the detection of BO from samples collected by Cytosponge

Study	N	Biomarker	Sensitivity	Specificity	AUC
Chettouh et al. (2017)[26]	278	TFIP	78.5%	96.9%	0.88
		TWIST1	69.8%	93.0%	0.81
		ZNF345	62.4%	100%	0.82
		ZNF569	59.1%	99.2%	0.79
Li et al. (2018)[28]	64	MIR7, 10a, 30a, 145, 181a, 192, 194, 196a, 199a, 199b, 215	83.9%	90.5%	0.87 (95% CI, 0.82 to 0.92)
		MIR7, 30a, 181a, 192, 196a, 199a	86.2%	91.6%	0.89 (95% CI, 0.84 to 0.93)
		MIR7, 30a, 181a, 192, 196a, 199a plus TFF3	NR	NR	0.92 (95% CI, 0.88 to 0.96)
		MIR192, 196a, 199a, plus TFF3	93.1%	93.7%	0.93 (95% CI, 0.90 to 0.97)
Abbreviations: AUC, area under the receiving operator curve; BO, Barrett Oesophagus; NR, not reported.					

Table C2: Diagnostic accuracy of biomarker candidates for distinction between non-dysplastic and dysplastic BO

Study	Biomarker	Sensitivity	Specificity
Ross-Innes et al. (2017)[30]	P53 immunohistochemistry	58% (44% to 70%)*	96% (92% to 98%)*
	TP53 mutation	58% (44% to 70%)*	85% (80% to 90%)*
	P53 abnormality	72% (58% to 83%)*	83% (77% to 88%)*
	Glandular atypia	64% (50% to 77%)*	94% (90% to 97%)*
	c-Myc immunohistochemistry	63% (49% to 75%)*	72% (66% to 78%)*
	Aurora kinase A immunohistochemistry	78% (65% to 88%)*	70% (64% to 77%)*
	MYOD1 methylation	67% (61% to 74%)*	64% (50% to 77%)*
	RUNX3 methylation	74% (67% to 79%)*	60% (46% to 73%)*
	Combined MYOD1 and RUNX3 methylation	70% (63% to 76%)*	62% (48% to 75%)*
Katz-Summercorn et al. (2017)[27]	A multi-gene panel covering >2800 COSMIC hotspot mutations in 50 oncogenes and tumour suppressor genes	71.4% (95% CI, 51.3% to 86.8%)	90.3% (95% CI, 74.3% to 98.0%)
* Data presented as median (interquartile range). Abbreviations: BO, Barrett oesophagus; COSMIC, Catalogue Of Somatic Mutations In Cancer.			

Table C3: Diagnostic accuracy of biomarker panels for risk stratification of patients with BO

Diagnostic accuracy parameters	Identification of high-grade dysplasia or cancer		Identification of dysplasia of any grade or cancer	
	Training cohort	Validation cohort	Training cohort	Validation cohort
Cytosponge biomarker-positive only				
AUROC	0.80 (0.75 to 0.85)	0.86 (0·81 to 0.92)	0.77 (0.73 to 0.81)	0.80 (0.74 to 0.86)
Sensitivity	74% (65% to 83%)	89% (77% to 97%)	65% (57% to 72%)	72% (61% to 83%)
Specificity	86% (83% to 89%)	84% (80% to 88%)	89% (87% to 92%)	88% (84% to 91%)
Cytosponge biomarker-positive plus clinical risk factors				
AUROC	0.87 (0.82 to 0.92)	0.91 (0.86 to 0.95)	0.83 (0.79 to 0.88)	0.84 (0.78 to 0.90)
Sensitivity	77% (68% to 86%)	80% (66% to 91%)	70% (63% to 78%)	69% (56% to 80%)

Specificity	86% (82% to 89%)	87% (83% to 91%)	86% (82% to 89%)	91% (88% to 94%)
Clinical risk factors only				
AUROC	0.69 (0.63 to 0.75)	0.72 (0.64 to 0.80)	0.67 (0.62 to 0.72)	0.68 (0.61 to 0.75)
Sensitivity	66% (57% to 76%)	91% (80% to 100%)	62% (53% to 69%)	80% (69% to 89%)
Specificity	65% (60% to 69%)	46% (40% to 51%)	65% (61% to 70%)	50% (44% to 56%)
Abbreviations: AUROC, area under the receiving operator curve; BO, Barrett oesophagus. Table adapted from Pilonis et al. (2022)[29].				

Table C4: Cost effectiveness of various strategies for the surveillance of BO

Surveillance strategy	Cost	QALY	ICER
No surveillance	US$8,792,073	11,734	—
Endoscopy only	US$12,364,203	11,839	Dominated
Alternating Cytosponge and endoscopy	US$11,192,561	11,842	Dominated
Endoscopy every third surveillance	US$10,778,010	11,843	Dominated
Cytosponge only	US$10,245,325	11,844	US$13,259 per QALY gained
Note: All numbers are reported per 1,000 patients. Abbreviations: BO, Barrett oesophagus; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year. Table adapted from Eluri et al. (2022)[24].			