National Institute for Health and Care Excellence

Final

Barrett's oesophagus and stage 1 oesophageal adenocarcinoma

[E] Evidence review for non-endoscopic surveillance techniques

NICE guideline NG231

No recommendations were made from this evidence review

February 2023

Final

National Institute for Health and Care Excellence

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Contents

1 Clinical and cost effectiveness of non-endoscopic surveillance techniques

1.1 Review question

For adults with Barrett's oesophagus, what is the clinical and cost effectiveness of different non-endoscopic surveillance techniques, including cytosponge?

1.1.1 Introduction

Endoscopic surveillance of Barrett's oesophagus has traditionally been performed using conventional upper gastrointestinal endoscopy with mapping biopsies. However, there have been recent developments of alternative approaches with the development of non-endoscopic cell collection devices, including cytosponge. These approaches are conceptually similar to a cervical smear, where a swallowed device is used to trawl the oesophagus to collect cells, which are then sent to a laboratory for cytological examination for the presence of dysplasia. Cases where abnormal cells are found are then referred for conventional endoscopic assessment. These techniques carry the potential benefit that they can be performed in a primary care setting by a Practice Nurse, do not require sedation and could potentially have a significant impact on the resource utilization and cost effectiveness of Barrett's surveillance, if found to be effective. Consequently, it is important to determine the clinical and cost effectiveness of non endoscopic surveillance techniques in the surveillance of patients with Barrett's metaplasia with no prior history of dysplasia.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults, 18 years and over, with non-dysplastic Barrett's oesophagus Exclusion: Adults with any level of dysplasia
Interventions	• Non endoscopic cell collection devices such as: o Cytosponge o Esopha cap o Balloon brush
Comparison	High resolution white light endoscopy
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Detection of any grade of dysplasia • Detection of early cancer or high-grade dysplasia • Health related quality of life • Adverse events (bleeding, perforation, pain) • Rate of inadequate sampling (requiring repeat or conversion) Time point: any time point available; no minimum follow-up
Study design	• RCT • If no RCT data is available, non-randomised studies will be considered if there is an active comparator within the study. • Systematic reviews of RCTs Published NMAs and IPDs will be considered for inclusion.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

No relevant clinical studies comparing non-endoscopic surveillance techniques with high resolution white-light endoscopy were included in the review.

See also the study selection flow chart in Appendix C.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix E.

1.1.5 Summary of the effectiveness evidence

There was no clinical evidence found.

1.1.6 Economic evidence

1.1.6.1 Included studies

No health economic studies were included.

1.1.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix D.

1.1.7 Summary of included economic evidence

There was no economic evidence found.

1.1.8 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.9 Unit costs

Table 2: Unit costs

Resource	Unit costs	Source
Cytosponge	£280	NICE Medtech innovation briefing [MIB240]
FE21Z: diagnostic endoscopic upper gastrointestinal tract procedure with biopsy	£554	National Schedule of Reference Costs 2019/20

2 Diagnostic accuracy of non-endoscopic surveillance techniques

2.1 Review question

What is the diagnostic accuracy of different non-endoscopic surveillance techniques including cytosponge?

2.1.1 Summary of the protocol

For full details see the review protocol in Appendix F.

Table 3: PICO characteristics of review question

Population	Adults, 18 years and over, with non-dysplastic Barrett's oesophagus or dysplastic BO (if less than 50% of study population)
Target condition	Barrett's oesophagus
Index tests	• Non endoscopic cell collection devices such as: o Cytosponge o Esophacap o Balloon brush
Reference standard	High resolution white light endoscopy with Seattle protocol biopsies
Outcomes	Detection of progression to any grade of dysplasia • Sensitivity • Specificity • Data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives).
Study design	Observational studies: • Cross-sectional studies • Prospective / Retrospective diagnostic studies • Systematic Reviews of observational studies Any study containing a diagnostic accuracy data or analysis

2.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

2.1.3 Diagnostic evidence

2.1.3.1 Included studies

Three studies were included in the review; [1, 2, 4] these are summarised below in Table 4. Evidence from these studies is summarised in the clinical evidence summary below in**Error! Reference source not found.** and references in 2.1.12

One prospective cohort study examined the diagnostic accuracy of balloon cytology for detecting high-grade dysplasia/adenocarcinoma and any grade of dysplasia or cancer.

One retrospective case-control study examined the diagnostic accuracy of Formalin-fixed, paraffin embedded (FFPE) cytosponge for detecting dysplasia in a sample of people with known dysplastic and non-dysplastic Barrett's oesophagus.

One multi-centre retrospective cross-sectional study examined the diagnostic accuracy of cytosponge coupled with laboratory biomarkers and clinical factors (overexpression of p53, cellular atypia and 17 clinical demographic variables e.g., age, BMI and smoking status) for detecting high-grade dysplasia/cancer and any grade of dysplasia or cancer

The sensitivity of tests was the most important measure in this review because the committee agreed the most important outcome is not to miss any cancer or progression to dysplasia which is associated with a significant risk of cancer for patients. Thus, sensitivity was prioritised for decision making. The committee set clinical decision thresholds as sensitivity/specificity =0.9 and 0.8 above which a test would be recommended and 0.6 and 0.5 below which a test is of no clinical use.

No relevant diagnostic test accuracy studies of Esophacap were identified.

See also the study selection flow chart in Appendix H, sensitivity and specificity and study evidence tables in Appendix I.

2.1.3.2 Excluded studies

See the excluded studies list in Appendix L.

2.1.4 Summary of studies included in the diagnostic evidence

Table 4: Summary of studies included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Falk 1997 [1]	Barrett's oesophagus patients with dysplasia enrolled in a cancer surveillance programme (n=63) Mean age (range): 61.3 (29-81) years USA	High grade dysplasia/ adenocarcinoma Any level of dysplasia	Balloon cytology	Histology (after cytological brushing and biopsy specimens)	Analysis was based on n=52 patients for which adequate columnar epithelium was obtained.
Katz 2017 [2]	Patients with non-dysplastic Barrett's oesophagus (n=31); age, median (range): 64 (16-81); Patients with dysplastic Barrett's oesophagus (n=28); age median (range): 66.5 (51-81) UK	Dysplasia	Formalin-fixed, paraffin embedded (FFPE) Cytosponge	Endoscopy and biopsy	Case-control study examining diagnostic accuracy for dysplastic vs non-dysplastic Barrett's oesophagus by detecting mutations using the Ion AmpliSeq Cancer Hotspot panel V2 on Cytosponge samples. Known dysplasia sample:10 LGD, 6 HGD, 12 intramucosal carcinoma samples
Pilonis 2022 [4]	People having endoscopic surveillance for Barrett's oesophagus (with intestinal metaplasia); divided into	High grade dysplasia or cancer Any grade of dysplasia or cancer	Cytosponge coupled with laboratory biomarkers and clinical factors	Endoscopy (with biopsy)	Retrospective multi-centre cross-sectional study, including a real-life prospective cohort of patients who had their Barrett's oesophagus

Study	Population	Target condition	Index test	Reference standard	Comments
	training cohort: n = 557; validation cohort: n=334 Age, mean (range): training cohort 65 (59-72); validation cohort 67 (58-73). UK		Cut-off for positivity: high risk (biomarker positive) and moderate risk (clinical risk factor; Barrett's oesophagus length, sex or age) vs low risk (neither clinical risk factor, nor pathology biomarkers present)		surveillance delayed due to decreased endoscopy provision during the COVID-19 pandemic (DELTA implementation study). Data for the prospective cohort have not yet been published as the study is still ongoing and hence are not part of the current evidence review. Included participants from the BEST2 and BEST 3 clinical trials. The study aimed to derive and evaluate cytosponge biomarkers and clinical risk factors to triage patients at high, moderate and low risk of Barrett's oesophagus-related neoplasia. Evaluated biomarkers were overexpression of p53, cellular atypia and 17 clinical demographic variables (e.g. age, BMI, smoking status)

See Appendix I for full evidence tables

2.1.5 Summary of the diagnostic evidence

Table 5: Clinical evidence summary: diagnostic test accuracy for cytosponge (vs endoscopy with high resolution Seattle protocol biopsies)

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
FFPE Cytosponge to detect dysplasia in people with known dysplastic and non-dysplastic Barrett's							
1 retrospective case-control study	59	Serious[1]	Not serious	Not serious	Serious [2]	Sensitivity=0.71 (0.51- 0.87)	LOW
		Serious[1]	Not serious	Not serious	Serious [2]	Specificity=0.90 (0.74- 0.98)	LOW
Cytosponge (with laboratory biomarkers) to detect high-grade dysplasia/cancer (training cohort)							
1 retrospective multi-centre cross-sectional study	557	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.74 (0.64 -0.83)	HIGH
		Not serious	Not serious	Not serious	Not serious	Specificity= 0.86 (0.83 -0.89)	HIGH
Cytosponge (with laboratory biomarkers) to detect high-grade dysplasia/cancer (validation cohort)							
1 retrospective multi-centre cross-sectional study	343	Not serious	Not serious	Not serious	Serious [2]	Sensitivity= 0.89 (0.73-0.97)	MODERATE
		Not serious	Not serious	Not serious	Not serious	Specificity= 0.84 (0.80-0.88)	HIGH
Cytosponge (with laboratory biomarkers) to detect any grade of dysplasia/cancer (training cohort)							
1 retrospective multi-centre cross-sectional study	557	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.65 (0.56 -0.73)	HIGH
		Not serious	Not serious	Not serious	Not serious	Specificity= 0.89 (0.86 -0.92)	HIGH
Cytosponge (with laboratory biomarkers) to detect any grade of dysplasia/cancer (validation cohort)							
1 retrospective multi-centre cross-sectional study	343	Not serious	Not serious	Not serious	Serious [2]	Sensitivity= 0.72 (0.59-0.82)	MODERATE
		Not serious	Not serious	Not serious	Not serious	Specificity= 0.88 (0.84-0.92)	HIGH

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment as the study was rated at high risk of bias, due unclear participant recruitment method .*

[2] *Imprecision was assessed based on inspection of the confidence intervals. For sensitivity, two clinical decision thresholds were determined at the value above which a test would be recommended (90%), and a second below which a test would be considered of no clinical use (60%). For specificity, two clinical decision thresholds were determined at the value above which a test would be recommended (80%), and a second below which a test would be considered of no clinical use (50%). The*

evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate crossed one threshold and downgraded by 2 increments when the range covered two thresholds.

Table 6: Clinical evidence summary: diagnostic test accuracy for balloon cytology (vs histology after cytological brushing and high-resolution biopsy specimens)

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Balloon cytology to detect high-grade dysplasia/adenocarcinoma in people with Barrett's oesophagus							
1 retrospective cohort study	52	Not serious	Not serious	Not serious	Very serious[1]	Sensitivity=0.80 (0.44- 0.97)	LOW
		Not serious	Not serious	Not serious	Not serious	Specificity=0.95 (0.84- 0.99)	HIGH
Balloon cytology to detect any level of dysplasia/ adenocarcinoma in people with Barrett's oesophagus							
1 retrospective cohort study	52	Not serious	Not serious	Not serious	Serious[1]	Sensitivity= 0.56 (0.31 -0.78)	MODERATE
		Not serious	Not serious	Not serious	Not serious	Specificity= 1.00 (0.90 -1.00)	HIGH
Balloon cytology to detect adenocarcinoma in people with Barrett's oesophagus (analysis excluding people with HGD, LGD, indefinite for dysplasia)							
1 retrospective cohort study	42	Not serious	Not serious	Not serious	Very Serious[1]	Sensitivity= 0.75 (0.35 -0.97)	LOW
		Not serious	Not serious	Not serious	Not serious	Specificity= 1.00 (0.90 -1.00)	HIGH
Balloon cytology to detect high-grade dysplasia in people with Barrett's oesophagus (analysis excluding people with adenocarcinoma, LGD, indefinite for dysplasia)							
1 retrospective cohort study	36	Not serious	Not serious	Not serious	Very Serious[1]	Sensitivity= 1.00 (0.16-1.00)	LOW
		Not serious	Not serious	Not serious	Not serious	Specificity= 1.00 (0.90-1.00)	HIGH
Balloon cytology to detect low-grade or indefinite dysplasia in people with Barrett's oesophagus (analysis excluding people with adenocarcinoma, HGD)							
1 retrospective cohort study	42	Not serious	Not serious	Not serious	Very Serious[2]	Sensitivity= 0.25 (0.03 -0.65)	LOW
		Not serious	Not serious	Not serious	Not serious	Specificity= 1.00 (0.90 -1.00)	HIGH

[1] Imprecision was assessed based on inspection of the confidence intervals. For sensitivity, two clinical decision thresholds were determined at the value above which a test would be recommended (90%), and a second below which a test would be considered of no clinical use (60%). For specificity, two clinical decision thresholds were determined at the value above which a test would be recommended (80%), and a second below which a test would be considered of no clinical use (50%). The evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate crossed one threshold and downgraded by 2 increments when the range covered two thresholds.

2.1.6 Economic evidence

2.1.6.1 Included studies

No health economic studies were included.

2.1.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix K.

2.1.7 Summary of included economic evidence

There was no economic evidence found.

2.1.8 Economic model

This area was prioritised for new cost-effectiveness analysis. However, original economic modelling was not conducted due to a lack of robust clinical evidence.

2.1.9 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 7: Unit costs

Resource	Unit costs	Source
Cytosponge	£280	NICE Medtech innovation briefing [MIB240]
FE21Z: diagnostic endoscopic upper gastrointestinal tract procedure with biopsy	£554	National Schedule of Reference Costs 2019/20

2.1.10 The committee's discussion and interpretation of the evidence

2.1.10.1 The outcomes that matter most

Intervention review:

The outcomes considered for this review were detection of any grade of dysplasia, detection of early cancer or high-grade dysplasia, health related quality of life, adverse events, rate of inadequate sampling (requiring repeat or conversion). For purposes of decision making, all outcomes were considered equally important and were therefore rated as critical by the committee. No evidence was identified for any of the outcomes.

Diagnostic review:

The committee considered the diagnostic measures of sensitivity and specificity of non-endoscopic techniques for detection of any grade of dysplasia in Barrett's oesophagus. The population of interest was people with non-dysplastic Barrett's oesophagus and the committee were interested in examining the accuracy of tests in detecting progression to low and high-grade dysplasia or cancer. The sensitivity of tests was the most important measure

in this review because the committee agreed the most important outcome is not to miss any cancer or progression to dysplasia which is associated with a significant risk of cancer for patients. Thus, sensitivity was prioritised for decision making. Clinical decision thresholds were set by the committee as sensitivity of 0.9 and specificity of 0.8 above which a test would be recommended and sensitivity of 0.6 and specificity of 0.5 below which a test is of no clinical use.

2.1.10.2 The quality of the evidence

Intervention review:

No relevant clinical studies were identified comparing the effectiveness of non-endoscopic surveillance techniques with high resolution white light endoscopy (with Seattle protocol biopsies). Studies were commonly excluded because of an incorrect population, looking at the detection of Barrett's oesophagus in a cohort of people with known Barrett's oesophagus compared with a cohort of people without the disease, or not reporting relevant outcomes.

Diagnostic review:

Clinical evidence for the diagnostic accuracy of non-endoscopic surveillance techniques was available from 3 studies. One retrospective case-control study on the diagnostic accuracy of cytosponge combined with a gene panel on DNA extracted from the Formalin-fixed, paraffin embedded (FFPE) specimens for detecting dysplasia. One multi-centre retrospective cross-sectional study on the diagnostic accuracy of cytosponge coupled with laboratory biomarkers and clinical factors for detecting high-grade dysplasia/cancer and any grade of dysplasia or cancer. One prospective cohort study on the diagnostic accuracy of balloon cytology for detecting high-grade dysplasia/adenocarcinoma and any grade of dysplasia or cancer.

The quality of the evidence for the cytosponge/gene panel was low, downgraded due to serious risk of bias (due to lack of clarity on the participant recruitment) and imprecision (with the range of the confidence interval crossing one clinical threshold for decision making). Evidence for the diagnostic accuracy of the cytosponge with laboratory biomarkers and clinical factors was of high quality across all outcomes. Evidence for Balloon cytology ranged from low to high across outcomes, mostly being low for sensitivity due to very serious imprecision (with the range of the confidence interval crossing two clinical thresholds for decision making).

No clinical evidence was identified on the diagnostic accuracy of the Esopha cap or other non-endoscopic cell collection devices.

2.1.10.3 Benefits and harms

Intervention review:

Despite the absence of clinical evidence examining the effectiveness of non-endoscopic surveillance techniques, the committee noted that cytosponge is currently being used in certain centres as part of an NHS-sponsored initiative and is currently being implemented in the NHS ahead of evidence and NICE recommendations due to pressures on the endoscopy services during the Covid-19 pandemic. The committee emphasised there is a high level of interest in the use of cytosponge amongst patients who do not tolerate endoscopy because it is a quicker and less invasive technique. They agreed data is not yet available to support its wider use in clinical practice. The committee noted that balloon brushing is an older technique that is not currently being used in clinical practice.

Diagnostic review:

Clinical evidence for the diagnostic accuracy of the cytosponge/gene panel showed relatively high sensitivity (0.71) but did not meet the threshold set for sensitivity, and a high specificity (0.90) exceeding the threshold. The committee emphasised that the results of the study on the FFPE were based on a gene panel (mutation analysis) which is unlikely to be recommended for routine use as it is likely to be very expensive.

Cytosponge with laboratory biomarkers had high diagnostic accuracy in detecting high-grade dysplasia/cancer and any grade of dysplasia/cancer but the sensitivity was not high enough to meet the clinical decision threshold. The committee noted cytosponge is more likely to be used in a lower risk group. Whilst agreeing results looked promising in regard to the diagnostic accuracy, they were based on a single non-randomised retrospective study and therefore conclusions could not be drawn with certainty. The committee acknowledged the use of cytosponge may be an option for patients not wanting endoscopy. Patients who have had cytosponge often prefer it and it has the potential to reduce the pressure in endoscopy services if found to be effective. However, the committee emphasised the current evidence base does not support its implementation in current practice and agreed it could not be recommended at the current time. The committee also agreed it would not be appropriate to make a research recommendation because of ongoing trials, and the evidence could be reviewed once they have been completed.

The committee raised that endoscopy (with biopsies) used as the current gold standard in current practice and the reference standard in the present review, is not perfect, and the diagnostic accuracy of cytosponge could in fact be higher than that of the current gold standard.

Evidence on balloon cytology showed a high specificity across outcomes and sensitivity was also high for detecting high-grade dysplasia/adenocarcinoma, but not high enough to reach the clinical decision threshold, and much lower for detecting any level of dysplasia/adenocarcinoma. The committee noted the evidence was derived from a very small study and there was imprecision in the effect estimates limiting the extent to which conclusions could be drawn from the study. The committee emphasised that this is an old technique that patients find difficult to tolerate and is not currently used in clinical practice and agreed not to make a recommendation for its use.

The committee discussed the lack of evidence for Esophacap and noted that although there was no published evidence to support its diagnostic accuracy currently, there is ongoing research on the Esopha cap that may potentially be useful in future updates of the guideline.

2.1.10.4 Cost effectiveness and resource use

Non-endoscopic surveillance techniques are generally cheaper than endoscopic procedures, easier to administer, and less invasive to the patient. Their effectiveness as a means of surveillance in Barrett's oesophagus, however, is unclear.

No economic evaluations were identified during the review.

The committee discussed the clinical evidence. They agreed that the evidence for the diagnostic accuracy of cytosponge was promising but noted it was based on a single non-randomised retrospective study and therefore conclusions could not be drawn with certainty. Since there was a lack of robust clinical evidence, they concluded that it would not be feasible to conduct a cost effectiveness analysis at this time.

The committee noted that CRUK and NIHR funding has been secured for a prospective study looking at cytosponge in surveillance and data should be available in 12 to 18 months. They agreed that more evidence was required and felt it best to wait for these results to be published.

2.1.11 Recommendations supported by this evidence review

No recommendations were made from this evidence review.

2.1.12 References

1. Falk GW, Chittajallu R, Goldblum JR, Biscotti CV, Geisinger KR, Petras RE et al. Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. Gastroenterology. 1997; 112(6):1787-1797

2. Katz-Summercorn A, Anand S, Ingledew S, Huang Y, Roberts T, Galeano-Dalmau N et al. Application of a multi-gene next-generation sequencing panel to a non-invasive oesophageal cell-sampling device to diagnose dysplastic Barrett's oesophagus. The Journal of Pathology Clinical Research. 2017; 3(4):258-267

3. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated January 2022]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

4. Pilonis ND, Killcoyne S, Tan WK, O'Donovan M, Malhotra S, Tripathi M et al. Use of a cytosponge biomarker panel to prioritise endoscopic Barrett's oesophagus surveillance: A cross-sectional study followed by a real-world prospective pilot. The Lancet Oncology. 2022; 23(2):270-278

Appendices

Appendix A – Review protocols

A.1 Review protocol for clinical and cost effectiveness of non-endoscopic surveillance techniques

ID	Field	Content
0.	PROSPERO registration number	CRD42022306158
1.	Review title	Clinical and cost effectiveness of non-endoscopic surveillance techniques
2.	Review question	For adults with Barrett's oesophagus, what is the clinical and cost effectiveness of different non-endoscopic surveillance techniques, including cytosponge?
3.	Objective	To assess the efficacy and cost effectiveness of different non-endoscopic surveillance techniques of people with Barrett's oesophagus
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies • Letters and comments are excluded

		Other searches: • Inclusion lists of systematic reviews will be checked by the reviewers The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Barrett's Oesophagus
6.	Population	Inclusion: Adults, 18 years and over, with non-dysplastic Barrett's oesophagus Exclusion: Adults with any level of dysplasia

7.	Intervention	• Non endoscopic cell collection devices such as:
		  ○ Cytosponge
		  ○ Esophacap
		  ○ Balloon brush
		•

8.	Comparator	• high resolution white light endoscopy

9.	Types of study to be included	• RCT • If no RCT data is available, non-randomised studies will be considered if there is an active comparator within the study. • Systematic reviews of RCTs Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Non comparative cohort studies Before and after studies Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Different non-endoscopic surveillance techniques are used for ongoing surveillance in people with Barrett's Oesophagus. This review aims to assess the clinical and cost effectiveness of the different techniques
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Detection of any grade of dysplasia • Detection of early cancer or high grade dysplasia • Health related quality of life • Adverse events (bleeding, perforation, pain) Rate of inadequate sampling (requiring repeat or conversion) Time point: any time point available; no minimum follow-up

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. This review will make use of the priority screening functionality within the EPPI-reviewer software. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0)

		Nonrandomised study, including cohort studies: Cochrane ROBINS-I Case control study: CASP case control checklist
16.	Strategy for data synthesis	Where available, outcome data from new studies will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available, WinBUGS will be used for network meta-analysis, if possible, given the data identified.
17.	Analysis of sub-groups	Stratification:

		Different non-endoscopic cell collection devices Subgrouping: If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: Short vs. long segment of Barrett's			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date				
22.	Anticipated completion date				
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☐

		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail @nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Norma O Flynn Gill Ritchie Amy Crisp		

		Lina Gulhane Stephen Deed Vimal Bedia Muksitur Rahman Melina Vasileiou Maheen Qureshi
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication

		• publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Barrett's Oesophagus	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken for all years using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later, that were included in the previous guidelines, will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014). [3] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as ‘Not applicable’.
- Studies published before 2006 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[3]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 8: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 April 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 April 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 4 of 12, April 2022 Cochrane Central Register of Controlled Trials to Issue 4 of 12, April 2022	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 26 April 2022	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	(intestin* adj2 metaplas*).ti,ab.
6.	or/1-5
7.	Precancerous conditions/
8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
9.	7 or 8
10.	exp Esophagus/
11.	Esophageal Mucosa/
12.	(oesophag* or esophag* or intramucosal* or intra-mucosal*).ti,ab.
13.	or/10-12
14.	9 and 13
15.	exp Esophageal Neoplasms/
16.	6 or 14 or 15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice or rodent*).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	Cytodiagnosis/
38.	((nonendoscop* or non endoscop* or minimal* invasive or noninvasive or non invasive or less invasive) adj3 (surveillanc* or approach* or screen* or monitor* or detect* or

	diagnos* or cytodiagnos* or cytolog* or assessment* or sampl* or collect* or brush* or biops* or examination* or test* or technique* or device* or tool* or capsule*)).ti,ab.
39.	((oesophag* or esophag* or cell*) adj3 (collect* or sampl* or device*)).ti,ab.
40.	(cytosponge* or esophacap* or esocheck* or aeonose* or balloon* or sponge* or electronic nose).ti,ab.
41.	or/37-40
42.	36 and 41
43.	Meta-Analysis/
44.	Meta-Analysis as Topic/
45.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
46.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
47.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
48.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
49.	(search* adj4 literature).ab.
50.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
51.	cochrane.jw.
52.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
53.	or/43-52
54.	randomized controlled trial.pt.
55.	controlled clinical trial.pt.
56.	randomi#ed.ab.
57.	placebo.ab.
58.	randomly.ab.
59.	clinical trials as topic.sh.
60.	trial.ti.
61.	or/54-60
62.	Epidemiologic studies/
63.	Observational study/
64.	exp Cohort studies/
65.	(cohort adj (study or studies or analys* or data)).ti,ab.
66.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
67.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
68.	Controlled Before-After Studies/
69.	Historically Controlled Study/
70.	Interrupted Time Series Analysis/
71.	(before adj2 after adj2 (study or studies or data)).ti,ab.
72.	exp case control study/
73.	case control*.ti,ab.
74.	Cross-sectional studies/
75.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
76.	or/62-75
77.	42 and (53 or 61 or 76)

Embase (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	(intestin* adj2 metaplas*).ti,ab.
6.	or/1-5
7.	Precancer/
8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
9.	7 or 8
10.	exp Esophagus/
11.	Esophagus Mucosa/
12.	(oesophag* or esophag*).ti,ab.
13.	or/10-12
14.	9 and 13
15.	exp Esophagus Tumor/
16.	6 or 14 or 15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	(conference abstract or conference paper).pt.
23.	or/17-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice or rodent*).ti.
33.	or/25-32
34.	16 not 33
35.	limit 34 to English language
36.	cytodiagnosis/
37.	esophageal cell sampling device/
38.	((nonendoscop* or non endoscop* or minimal* invasive or noninvasive or non invasive or less invasive) adj3 (surveillanc* or approach* or screen* or monitor* or detect* or diagnos* or cytodiagnos* or cytolog* or assessment* or sampl* or collect* or brush* or biops* or examination* or test* or technique* or device* or tool* or capsule*)).ti,ab.
39.	((oesophag* or esophag* or cell*) adj3 (collect* or sampl* or device*)).ti,ab.

40.	(cytosponge* or esophacap* or esocheck* or aeonose* or balloon* or sponge* or electronic nose).ti,ab.
41.	or/36-40
42.	35 and 41
43.	random*.ti,ab.
44.	factorial*.ti,ab.
45.	(crossover* or cross over*).ti,ab.
46.	((doubl* or singl*) adj blind*).ti,ab.
47.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
48.	crossover procedure/
49.	single blind procedure/
50.	randomized controlled trial/
51.	double blind procedure/
52.	or/43-51
53.	Systematic Review/
54.	Meta-Analysis/
55.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
56.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
57.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
58.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
59.	(search* adj4 literature).ab.
60.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
61.	cochrane.jw.
62.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
63.	or/53-62
64.	Clinical study/
65.	Observational study/
66.	Family study/
67.	Longitudinal study/
68.	Retrospective study/
69.	Prospective study/
70.	Cohort analysis/
71.	Follow-up/
72.	cohort*.ti,ab.
73.	71 and 72
74.	(cohort adj (study or studies or analys* or data)).ti,ab.
75.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
76.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
77.	(before adj2 after adj2 (study or studies or data)).ti,ab.
78.	exp case control study/
79.	case control*.ti,ab.

80.	cross-sectional study/
81.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
82.	or/64-70,73-81
83.	42 and (52 or 63 or 82)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Barrett Esophagus] explode all trees
#2.	barrett*:ti,ab
#3.	speciali* near/3 (epithel* or oesophag* or esophag* or mucos*):ti,ab
#4.	column* near/3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*):ti,ab
#5.	(intestin* near/2 metaplas*):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Precancerous Conditions] explode all trees
#8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*):ti,ab
#9.	#7 or #8
#10.	MeSH descriptor: [Esophagus] explode all trees
#11.	MeSH descriptor: [Esophageal Mucosa] explode all trees
#12.	(oesophag* or esophag* or intramucosal* or intra-mucosal*):ti,ab
#13.	(or #10-#12)
#14.	#9 and #13
#15.	MeSH descriptor: [Esophageal Neoplasms] explode all trees
#16.	#6 or #14 or #15
#17.	MeSH descriptor: [Cytodiagnosis] this term only
#18.	((nonendoscop* or non endoscop* or minimal* invasive or noninvasive or non invasive or less invasive) near/3 (surveillanc* or approach* or screen* or monitor* or detect* or diagnos* or cytodiagnos* or cytolog* or assessment* or sampl* or collect* or brush* or biops* or examination* or test* or technique* or device* or tool* or capsule*)):ti,ab
#19.	((oesophag* or esophag* or cell*) near/3 (collect* or sampl* or device*)):ti,ab
#20.	(cytosponge* or esophacap* or esocheck* or aeonose* or balloon* or sponge* or (electronic nose)):ti,ab
#21.	(or #17-#20)
#22.	#16 and #21
#23.	conference:pt or (clinicaltrials or trialsearch):so
#24.	#22 not #23

Epistemonikos search terms

1.	(title:(Barrett* OR "oesophageal adenocarcinoma*" OR "esophageal adenocarcinoma*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "oesophageal carcinoma*" OR "esophageal carcinoma*" OR "oesophageal metaplas*" OR "esophageal dysplas*" OR "column* epithel*" OR "intestin* metaplas*" OR "intestin* dysplas*") OR abstract:(Barrett* OR "oesophageal adenocarcinoma*" OR "esophageal adenocarcinoma*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "oesophageal carcinoma*" OR "esophageal carcinoma*" OR "oesophageal metaplas*" OR "esophageal dysplas*" OR "column* epithel*" OR "intestin* metaplas*" OR "intestin* dysplas*")) AND (title:("non-endoscopic*" OR nonendoscopic* OR cytosponge* OR esophacap* OR esocheck* OR balloon OR sponge OR "cell collection

	sampling device*") OR abstract:("non-endoscopic*" OR nonendoscopic* OR cytosponge* OR esophacap* OR esocheck* OR balloon OR sponge OR "cell collection sampling device*")

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Barrett's Oesophagus population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 9: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 April 2022	
Embase (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 April 2022	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 April 2022	English language

Medline (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	or/1-4
6.	Precancerous conditions/
7.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
8.	6 or 7
9.	exp Esophagus/
10.	Esophageal Mucosa/
11.	(oesophag* or esophag* or intramucosal* or intra-mucosal*).ti,ab.
12.	or/9-11
13.	8 and 12
14.	exp Esophageal Neoplasms/
15.	5 or 13 or 14
16.	letter/
17.	editorial/
18.	news/
19.	exp historical article/
20.	Anecdotes as Topic/
21.	comment/
22.	case report/
23.	(letter or comment*).ti.
24.	or/16-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animals/ not humans/
28.	exp Animals, Laboratory/
29.	exp Animal Experimentation/
30.	exp Models, Animal/
31.	exp Rodentia/
32.	(rat or rats or mouse or mice or rodent*).ti.
33.	or/26-32
34.	15 not 33
35.	limit 34 to English language
36.	economics/
37.	value of life/
38.	exp "costs and cost analysis"/

39.	exp Economics, Hospital/
40.	exp Economics, medical/
41.	Economics, nursing/
42.	economics, pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp budgets/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/36-51
53.	quality-adjusted life years/
54.	sickness impact profile/
55.	(quality adj2 (wellbeing or well being)).ti,ab.
56.	sickness impact profile.ti,ab.
57.	disability adjusted life.ti,ab.
58.	(qal* or qtime* or qwb* or daly*).ti,ab.
59.	(euroqol* or eq5d* or eq 5*).ti,ab.
60.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
61.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
62.	(hui or hui1 or hui2 or hui3).ti,ab.
63.	(health* year* equivalent* or hye or hyes).ti,ab.
64.	discrete choice*.ti,ab.
65.	rosser.ti,ab.
66.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
67.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
68.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
69.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
70.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
71.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
72.	or/53-71
73.	35 and (52 or 72)

Embase (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.

4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	or/1-4
6.	Precancer/
7.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
8.	6 or 7
9.	exp Esophagus/
10.	Esophagus Mucosa/
11.	(oesophag* or esophag*).ti,ab.
12.	or/9-11
13.	8 and 12
14.	exp Esophagus Tumor/
15.	5 or 13 or 14
16.	letter.pt. or letter/
17.	note.pt.
18.	editorial.pt.
19.	case report/ or case study/
20.	(letter or comment*).ti.
21.	(conference abstract or conference paper).pt.
22.	or/16-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/24-31
33.	15 not 32
34.	limit 33 to English language
35.	health economics/
36.	exp economic evaluation/
37.	exp health care cost/
38.	exp fee/
39.	budget/
40.	funding/
41.	budget*.ti,ab.
42.	cost*.ti.
43.	(economic* or pharmaco?economic*).ti.
44.	(price* or pricing*).ti,ab.

45.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
46.	(financ* or fee or fees).ti,ab.
47.	(value adj2 (money or monetary)).ti,ab.
48.	or/35-47
49.	quality-adjusted life years/
50.	"quality of life index"/
51.	short form 12/ or short form 20/ or short form 36/ or short form 8/
52.	sickness impact profile/
53.	(quality adj2 (wellbeing or well being)).ti,ab.
54.	sickness impact profile.ti,ab.
55.	disability adjusted life.ti,ab.
56.	(qal* or qtime* or qwb* or daly*).ti,ab.
57.	(euroqol* or eq5d* or eq 5*).ti,ab.
58.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
59.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
60.	(hui or hui1 or hui2 or hui3).ti,ab.
61.	(health* year* equivalent* or hye or hyes).ti,ab.
62.	discrete choice*.ti,ab.
63.	rosser.ti,ab.
64.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
65.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
66.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
67.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
68.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
69.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
70.	or/49-69
71.	34 and (48 or 70)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#2.	(barrett*)
#3.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions EXPLODE ALL TREES
#7.	((dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma*or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*))
#8.	#6 OR #7
#9.	MeSH DESCRIPTOR Esophagus EXPLODE ALL TREES
#10.	MeSH DESCRIPTOR Esophageal Mucosa EXPLODE ALL TREES
#11.	(oesophag* or esophag* or intramucosal* or intra-mucosal*)
#12.	#9 OR #10 OR #11

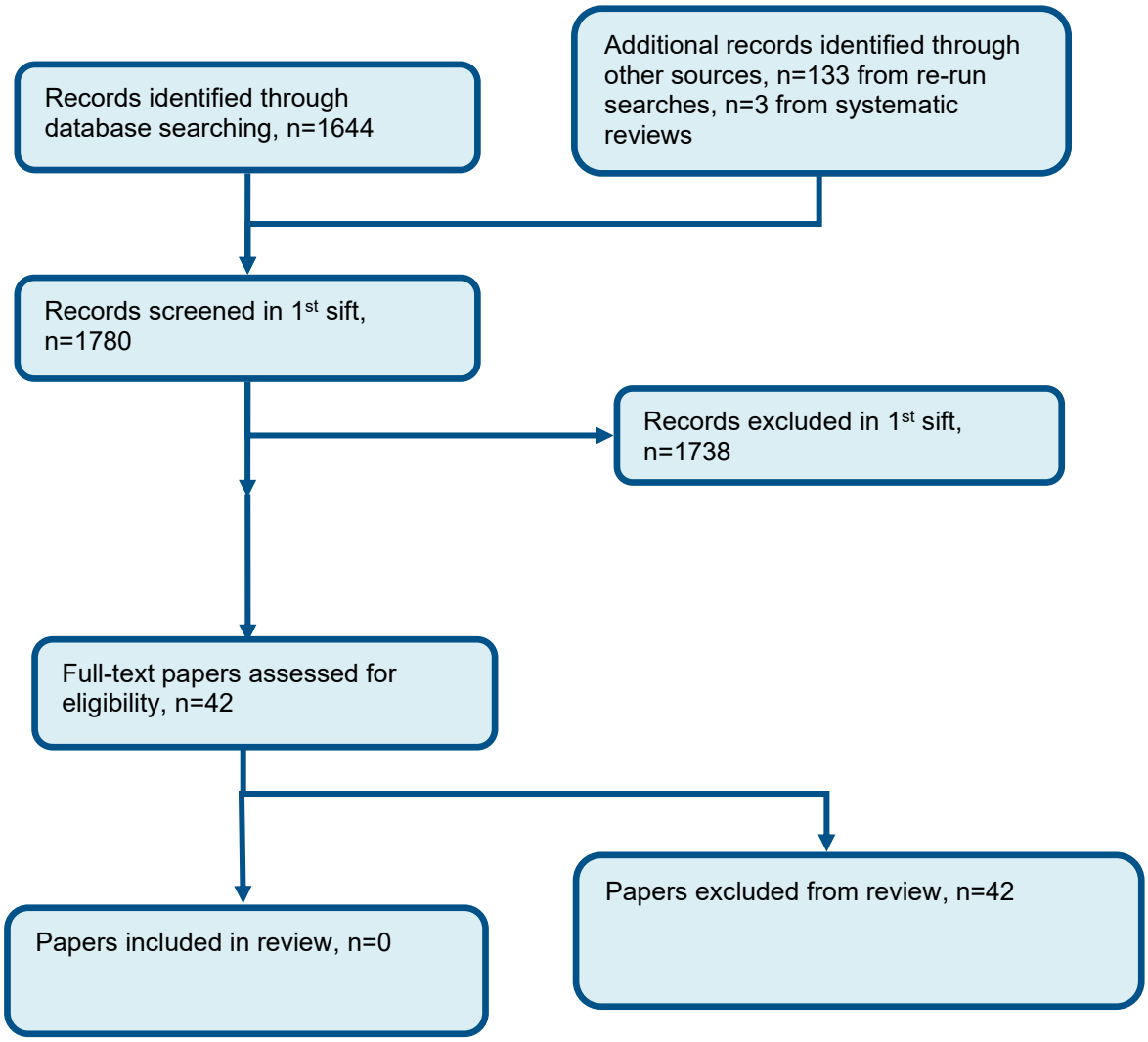
#13.	#8 AND #12
#14.	#5 OR #13
#15.	MeSH DESCRIPTOR Esophageal Neoplasms EXPLODE ALL TREES
#16.	#14 OR #15

INAHTA search terms

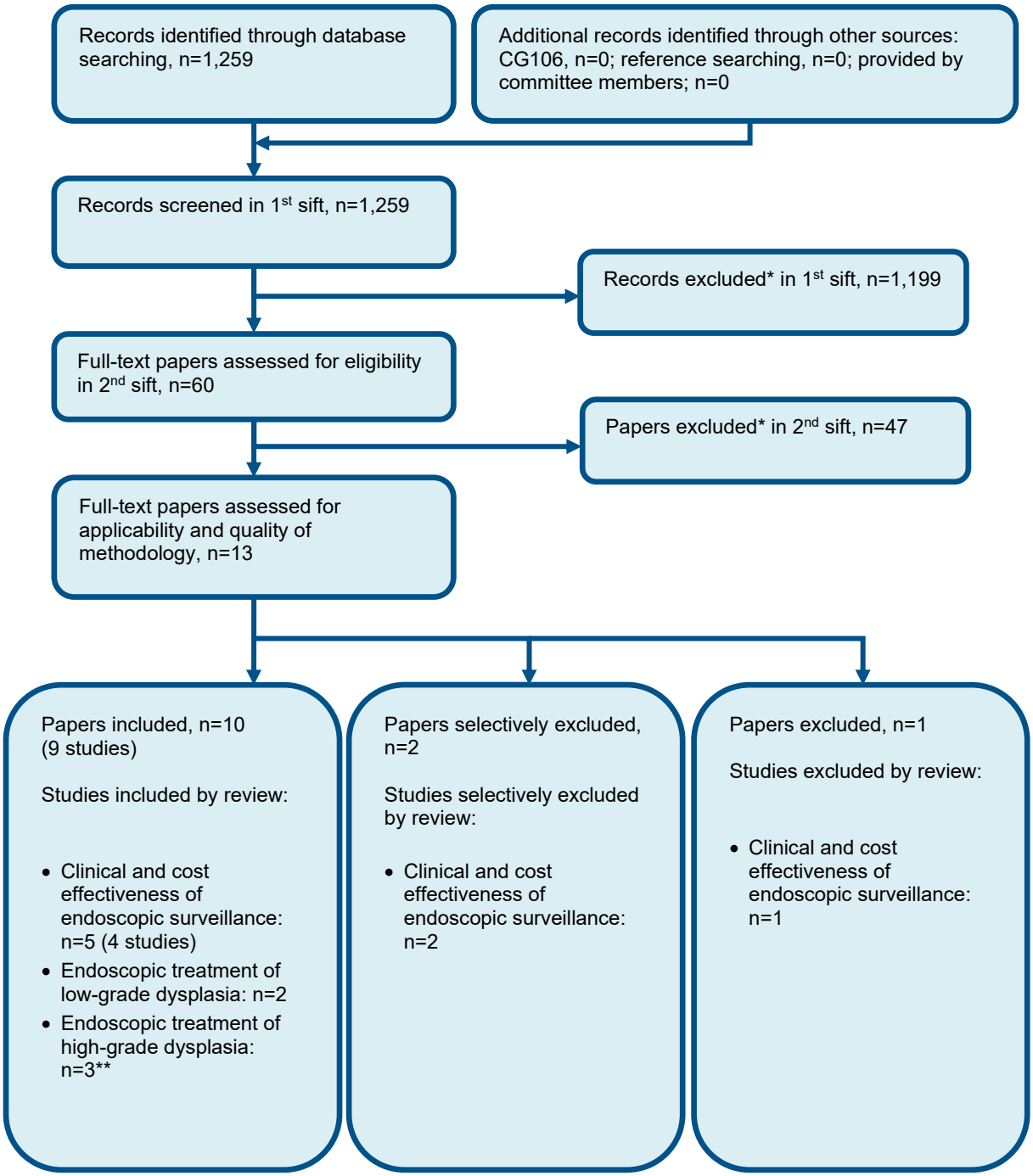
1.	("Barrett Esophagus"[mh]) OR (Barrett*) OR (Esophageal Neoplasms)[mh]

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of Non-endoscopic surveillance techniques



Appendix D – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
** One article identified was applicable to endoscopic treatment of low-grade dysplasia and endoscopic treatment for high-grade dysplasia, for the purposes of this diagram they have been included under endoscopic treatment of low-grade dysplasia only.

Appendix E – Excluded studies

Clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Borovicka, J., Schönegg, R., Hell, M. et al. (2009) Is there an advantage to be gained from adding digital image cytometry of brush cytology to a standard biopsy protocol in patients with Barrett's esophagus?. Endoscopy 41(5): 409-414	- Study does not contain an intervention relevant to this review protocol *examines endoscopic techniques*
Chen, B. L., Xing, X. B., Wang, J. H. et al. (2014) Improved biopsy accuracy in Barrett's esophagus with a transparent cap. World Journal of Gastroenterology 20(16): 4718-4722	- Population not relevant to this review protocol *People with suspected, not confirmed Barrett's oesophagus* - No relevant outcomes
Chernin, M. M., Amberg, J. R., Kogan, F. J. et al. (1986) Efficacy of radiologic studies in the detection of Barrett's esophagus. AJR. American Journal of Roentgenology 147(2): 257-260	- Population not relevant to this review protocol *Control group did not have Barrett's oesophagus.*
Dawsey, S. M., Shen, Q., Nieberg, R. K. et al. (1997) Studies of esophageal balloon cytology in Linxian, China. Cancer Epidemiology, Biomarkers & Prevention 6(2): 121-30	- Comparator in study does not match that specified in this review protocol
di Pietro, M. and Fitzgerald, R. C. (2013) Screening and risk stratification for Barrett's esophagus: how to limit the clinical impact of the increasing incidence of esophageal adenocarcinoma. Gastroenterology Clinics of North America 42(1): 155-73	- Review article but not a systematic review *potentially relevant references checked for inclusion*
Duvvuri, A., Desai, M., Vennelaganti, S. et al. (2021) Diagnostic accuracy of a novel third generation esophageal capsule as a non-invasive detection method for Barrett's esophagus: A pilot study. Journal of Gastroenterology and Hepatology (Australia) 36(5): 1222-1225	- No relevant outcomes *; no comparison group*

Study	Exclusion reason
Falk, G. W., Chittajallu, R., Goldblum, J. R. et al. (1997) Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. Gastroenterology 112(6): 1787-97	- *No relevant outcomes*
Gehrung, M., Crispin-Ortuzar, M., Berman, A. G. et al. (2021) Triage-driven diagnosis of Barrett's esophagus for early detection of esophageal adenocarcinoma using deep learning. Nature Medicine 27(5): 833-841	- No relevant outcomes
Grooteman, K. V., Wong Kee Song, L. M., Vleggaar, F. P. et al. (2017) Non-adherence to the rule of 3 does not increase the risk of adverse events in esophageal dilation. Gastrointestinal Endoscopy 85(2): 332-337.e1	- Comparator in study does not match that specified in this review protocol *Observational study with no comparison group.*
Haisley, K. R., Dolan, J. P., Olson, S. B. et al. (2017) Sponge Sampling with Fluorescent In Situ Hybridization as a Screening Tool for the Early Detection of Esophageal Cancer. Journal of Gastrointestinal Surgery 21(2): 215-221	- Population not relevant to this review protocol *Includes people with a history of gastroesophageal reflux disease, 10 of which had dysplasia at baseline, 19 had normal findings and only 20 had metaplasia (i.e. non-dysplastic Barrett's oesophagus)*
Iqbal, U., Siddique, O., Ovalle, A. et al. (2018) Safety and efficacy of a minimally invasive cell sampling device ('Cytosponge') in the diagnosis of esophageal pathology: a systematic review. European Journal of Gastroenterology & Hepatology 30(11): 1261-1269	- Systematic review used as source of primary studies
Iyer, P. G., Taylor, W. R., Johnson, M. L. et al. (2020) Accurate Nonendoscopic Detection of Barrett's Esophagus by Methylated DNA Markers: A Multisite Case Control Study. The American Journal of Gastroenterology 115(8): 1201-1209	- Population not relevant to this review protocol *compares technique on relevant population to the technique on control group not meeting protocol.*
Iyer, P. G., Taylor, W. R., Johnson, M. L. et al. (2018) Highly Discriminant Methylated DNA Markers for the Non-endoscopic Detection of Barrett's Esophagus. American Journal of Gastroenterology 113(8): 1156-1166	- Population not relevant to this review protocol *compares technique on relevant population to the technique on control group not meeting protocol.*
Iyer, P. G., Taylor, W. R., Slettedahl, S. W. et al. (2021) Validation of a methylated DNA marker panel for the nonendoscopic detection of	- Population not relevant to this review protocol

Study	Exclusion reason
Barrett's esophagus in a multisite case-control study. Gastrointestinal Endoscopy 94(3): 498-505	*compares technique on relevant population to the technique on control group not meeting protocol.* - No relevant outcomes
Januszewicz, W., Tan, W. K., Lehovsky, K. et al. (2018) Safety and acceptability of a non-endoscopic esophageal sampling device - Cytosponge®: a systematic review of multi-center data. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association	- Systematic review used as source of primary studies *Systematic review of studies including populations that do not meet protocol.*
Januszewicz, W., Tan, W. K., Lehovsky, K. et al. (2019) Safety and Acceptability of Esophageal Cytosponge Cell Collection Device in a Pooled Analysis of Data From Individual Patients. Clinical Gastroenterology & Hepatology 17(4): 647-656.e1	- Systematic review used as source of primary studies *review of prospective studies whose population did not meet protocol*
Kadri, S. R., Lao-Sirieix, P., O'Donovan, M. et al. (2010) Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. BMJ 341: c4372	- No relevant outcomes *diagnosis of Barrett's oesophagus; population did not have confirmed Barrett's at the time of testing.*
Katz-Summercorn, A., Anand, S., Ingledew, S. et al. (2017) Application of a multi-gene next-generation sequencing panel to a non-invasive oesophageal cell-sampling device to diagnose dysplastic Barrett's oesophagus. The Journal of Pathology. Clinical Research 3(4): 258-267	- No relevant outcomes
Konda, V. J. A. and Souza, R. F. (2018) Biomarkers of Barrett's Esophagus: From the Laboratory to Clinical Practice. Digestive Diseases & Sciences 63(8): 2070-2080	- Systematic review used as source of primary studies
Leoni-Parvex, S., Mihaescu, A., Pellanda, A. et al. (2000) Esophageal cytology in the follow-up of patients with treated upper aerodigestive tract malignancies. Cancer 90(1): 10-6	- No relevant outcomes
Muriithi, R. W.; Muchiri, L. W.; Lule, G. N. (2014) Esophageal cytology sponge diagnostic test results in kenyatta national referral hospital, kenya. Acta Cytologica 58(5): 483-8	- Population not relevant to this review protocol

Study	Exclusion reason
Pless, T. K.; Wara, P.; Kruse, A. (1996) Endoscopic treatment of oesophagoairway fistula with oesophageal balloon prosthesis. European Journal of Surgery 162(12): 957-9	- Population not relevant to this review protocol *patients with malignant diseases not limited to the oesophagus*
Ross-Innes, C. S., Chettouh, H., Achilleos, A. et al. (2017) Risk stratification of Barrett's oesophagus using a non-endoscopic sampling method coupled with a biomarker panel: a cohort study. The Lancet. Gastroenterology & Hepatology 2(1): 23-31	- No relevant outcomes *outcome is risk stratification of dysplasia based on computing the probability using cytosponge and clinical and molecular biomarkers.*
Ross-Innes, C. S., Debiram-Beecham, I., O'Donovan, M. et al. (2015) Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multi-center case-control study. PLoS Medicine / Public Library of Science 12(1): e1001780	- No relevant outcomes *the study looks at diagnostic accuracy of cytosponge in detecting Barrett's oesophagus in a cohort of people with Barrett's and controls with dyspepsia.* - Comparator in study does not match that specified in this review protocol
Saad, R. S., Mahood, L. K., Clary, K. M. et al. (2003) Role of cytology in the diagnosis of Barrett's esophagus and associated neoplasia. Diagnostic Cytopathology 29(3): 130-5	- Population not relevant to this review protocol *only 43% matched protocol*
Sharma, P., Wani, S., Rastogi, A. et al. (2008) The diagnostic accuracy of esophageal capsule endoscopy in patients with gastroesophageal reflux disease and Barrett's esophagus: a blinded, prospective study. American Journal of Gastroenterology 103(3): 525-32	- No relevant outcomes
Swart, N., Maroni, R., Muldrew, B. et al. (2021) Economic evaluation of Cytosponge R-trefoil factor 3 for Barrett esophagus: A cost-utility analysis of randomised controlled trial data. EClinicalMedicine 37: 100969	- Economic paper highlighted for inclusion in cost-effectiveness
Trindade, A. J., Navaneethan, U., Aslanian, H. R. et al. (2019) Advances in the diagnosis and surveillance of Barrett's esophagus (with videos). Gastrointestinal Endoscopy 90(3): 325-334	- Review article but not a systematic review *references for cytosponge checked*
Vogt, N., Schönegg, R., Gschossmann, J. M. et al. (2010) Benefit of baseline cytometry for	- Study does not contain an intervention relevant to this review protocol

Study	Exclusion reason
surveillance of patients with Barrett's esophagus. Surgical Endoscopy 24(5): 1144-1150	*examines an endoscopic technique*
Wang, W. L., Chang, I. W., Chang, C. Y. et al. (2014) Circumferential balloon-based radiofrequency ablation for ultralong and extensive flat esophageal squamous neoplasia. Gastrointestinal Endoscopy 80(6): 1185-9	- Population not relevant to this review protocol *squamous cell neoplasia*
Yusuf, A. and Fitzgerald, R. C. (2021) Screening for Barrett's Oesophagus: Are We Ready for it?. Current Treatment Options in Gastroenterology: 1-16	- Systematic review used as source of primary studies

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix F – Review protocols

F.1 Review protocol for diagnostic accuracy of non-endoscopic surveillance techniques

ID	Field	Content
0.	PROSPERO registration number	CRD42022315276
1.	Review title	Diagnostic accuracy of non-endoscopic surveillance techniques
2.	Review question	What is the diagnostic accuracy of different non-endoscopic surveillance techniques including cytosponge?
3.	Objective	To determine the accuracy of different non-endoscopic surveillance techniques in people with Barrett's oesophagus.
4.	Searches	The following databases (from inception) will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language studies Human studies Letters and comments are excluded Other searches: Inclusion lists of systematic reviews will be checked by the reviewers

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Barrett's oesophagus
6.	Population	Inclusion: Adults, 18 years and over, with non-dysplastic Barrett's oesophagus or dysplastic BO (if less than 50% of study population)

7.	Test	• Non endoscopic cell collection devices such as:
		  ○ Cytosponge
		  ○ Esophacap
		  ○ Balloon brush

8.	Reference standard	• high resolution white light endoscopy with Seattle protocol biopsies
9.	Types of study to be included	Observational studies: • Cross-sectional studies

		• Prospective / Retrospective diagnostic studies • Systematic Reviews of observational studies Any study containing a diagnostic accuracy data or analysis
10.	Other exclusion criteria	Studies that do not report sensitivity and specificity, or insufficient data to derive these values. Non-English language studies. Before and after studies Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Different non-endoscopic surveillance techniques could potentially be applicable to surveillance or monitoring surveillance in people with Barrett's Oesophagus. This review aims to assess the diagnostic accuracy of the different techniques in comparison to what is held as the gold standard (High resolution white light endoscopy)
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: Detection of progression to any grade of dysplasia • Sensitivity • Specificity • Data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives).
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.

		This review will make use of the priority screening functionality within the EPPI-reviewer software. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
14.	Risk of bias (quality) assessment	Risk of bias quality assessment will be assessed using QUADAS-2 checklist
15.	Strategy for data synthesis	Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention

		will be placed on sensitivity, determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.	
16.	Analysis of sub-groups	Stratification: Different non-endoscopic cell collection devices Dysplastic vs non-dysplastic Barrett's Subgrouping: If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: Short vs. long segment of Barrett's Grade of dysplasia (low, high, OAC)	
17.	Type and method of review	☐	Intervention
		☒	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	

20.	Anticipated or actual start date			
21.	Anticipated completion date			
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Guideline email]@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		

24.	Review team members	From the National Guideline Centre: Amy Crisp Gill Ritchie Lina Gulhane Muksitar Rahman Stephen Deed Maheen Qureshi Melina Vasileiou
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
28.	Other registration details	
29.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:

		• notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Barrett's oesophagus	
32.	Details of existing review of same topic by same authors		
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information		
35.	Details of final publication	www.nice.org.uk	

F.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken for all years using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later, that were included in the previous guidelines, will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014). [3] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as ‘Not applicable’.
- Studies published before 2006 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix G – Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual. [3]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

G.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 11: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 April 2022	Randomised controlled trials Systematic review studies Observational studies Diagnostic studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 April 2022	Randomised controlled trials Systematic review studies Observational studies Diagnostic studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 4 of 12, April 2022 Cochrane Central Register of Controlled Trials to Issue 4 of 12, April 2022	Exclusions (clinical trials, conference abstracts)
Epistemonikos	Inception to 26 April 2022	Systematic review

Database	Dates searched	Search filter used
(The Epistemonikos Foundation)		Exclusions (Cochrane reviews)

Medline (Ovid) search terms

78.	exp Barrett esophagus/
79.	barrett*.ti,ab.
80.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
81.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
82.	(intestin* adj2 metaplas*).ti,ab.
83.	or/1-5
84.	Precancerous conditions/
85.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
86.	7 or 8
87.	exp Esophagus/
88.	Esophageal Mucosa/
89.	(oesophag* or esophag* or intramucosal* or intra-mucosal*).ti,ab.
90.	or/10-12
91.	9 and 13
92.	exp Esophageal Neoplasms/
93.	6 or 14 or 15
94.	letter/
95.	editorial/
96.	news/
97.	exp historical article/
98.	Anecdotes as Topic/
99.	comment/
100.	case report/
101.	(letter or comment*).ti.
102.	or/17-24
103.	randomized controlled trial/ or random*.ti,ab.
104.	25 not 26
105.	animals/ not humans/
106.	exp Animals, Laboratory/
107.	exp Animal Experimentation/
108.	exp Models, Animal/
109.	exp Rodentia/
110.	(rat or rats or mouse or mice or rodent*).ti.
111.	or/27-33
112.	16 not 34
113.	limit 35 to English language

114.	Cytodiagnosis/
115.	((nonendoscop* or non endoscop* or minimal* invasive or noninvasive or non invasive or less invasive) adj3 (surveillanc* or approach* or screen* or monitor* or detect* or diagnos* or cytodiagnos* or cytolog* or assessment* or sampl* or collect* or brush* or biops* or examination* or test* or technique* or device* or tool* or capsule*)).ti,ab.
116.	((oesophag* or esophag* or cell*) adj3 (collect* or sampl* or device*)).ti,ab.
117.	(cytosponge* or esophacap* or esocheck* or aeonose* or balloon* or sponge* or electronic nose).ti,ab.
118.	or/37-40
119.	36 and 41
120.	Meta-Analysis/
121.	Meta-Analysis as Topic/
122.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
123.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
124.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
125.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
126.	(search* adj4 literature).ab.
127.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
128.	cochrane.jw.
129.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
130.	or/43-52
131.	randomized controlled trial.pt.
132.	controlled clinical trial.pt.
133.	randomi#ed.ab.
134.	placebo.ab.
135.	randomly.ab.
136.	clinical trials as topic.sh.
137.	trial.ti.
138.	or/54-60
139.	Epidemiologic studies/
140.	Observational study/
141.	exp Cohort studies/
142.	(cohort adj (study or studies or analys* or data)).ti,ab.
143.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
144.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
145.	Controlled Before-After Studies/
146.	Historically Controlled Study/
147.	Interrupted Time Series Analysis/
148.	(before adj2 after adj2 (study or studies or data)).ti,ab.
149.	exp case control study/
150.	case control*.ti,ab.
151.	Cross-sectional studies/

152.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
153.	or/62-75
154.	exp "sensitivity and specificity"/
155.	(sensitivity or specificity).ti,ab.
156.	((pre test or pretest or post test) adj probability).ti,ab.
157.	(predictive value* or PPV or NPV).ti,ab.
158.	likelihood ratio*.ti,ab.
159.	likelihood function/
160.	((area under adj4 curve) or AUC).ti,ab.
161.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
162.	gold standard.ab.
163.	exp Diagnostic errors/
164.	(false positiv* or false negativ*).ti,ab.
165.	Diagnosis, Differential/
166.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
167.	or/77-89
168.	42 and (53 or 61 or 76 or 90)

Embase (Ovid) search terms

84.	exp Barrett esophagus/
85.	barrett*.ti,ab.
86.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
87.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
88.	(intestin* adj2 metaplas*).ti,ab.
89.	or/1-5
90.	Precancer/
91.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
92.	7 or 8
93.	exp Esophagus/
94.	Esophagus Mucosa/
95.	(oesophag* or esophag*).ti,ab.
96.	or/10-12
97.	9 and 13
98.	exp Esophagus Tumor/
99.	6 or 14 or 15
100.	letter.pt. or letter/
101.	note.pt.
102.	editorial.pt.
103.	case report/ or case study/
104.	(letter or comment*).ti.
105.	(conference abstract or conference paper).pt.
106.	or/17-22

107.	randomized controlled trial/ or random*.ti,ab.
108.	23 not 24
109.	animal/ not human/
110.	nonhuman/
111.	exp Animal Experiment/
112.	exp Experimental Animal/
113.	animal model/
114.	exp Rodent/
115.	(rat or rats or mouse or mice or rodent*).ti.
116.	or/25-32
117.	16 not 33
118.	limit 34 to English language
119.	cytodiagnosis/
120.	esophageal cell sampling device/
121.	((nonendoscop* or non endoscop* or minimal* invasive or noninvasive or non invasive or less invasive) adj3 (surveillanc* or approach* or screen* or monitor* or detect* or diagnos* or cytodiagnos* or cytolog* or assessment* or sampl* or collect* or brush* or biops* or examination* or test* or technique* or device* or tool* or capsule*)).ti,ab.
122.	((oesophag* or esophag* or cell*) adj3 (collect* or sampl* or device*)).ti,ab.
123.	(cytosponge* or esophacap* or esocheck* or aeonose* or balloon* or sponge* or electronic nose).ti,ab.
124.	or/36-40
125.	35 and 41
126.	random*.ti,ab.
127.	factorial*.ti,ab.
128.	(crossover* or cross over*).ti,ab.
129.	((doubl* or singl*) adj blind*).ti,ab.
130.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
131.	crossover procedure/
132.	single blind procedure/
133.	randomized controlled trial/
134.	double blind procedure/
135.	or/43-51
136.	Systematic Review/
137.	Meta-Analysis/
138.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
139.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
140.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
141.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
142.	(search* adj4 literature).ab.
143.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
144.	cochrane.jw.
145.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.

146.	or/53-62
147.	Clinical study/
148.	Observational study/
149.	Family study/
150.	Longitudinal study/
151.	Retrospective study/
152.	Prospective study/
153.	Cohort analysis/
154.	Follow-up/
155.	cohort*.ti,ab.
156.	71 and 72
157.	(cohort adj (study or studies or analys* or data)).ti,ab.
158.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
159.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
160.	(before adj2 after adj2 (study or studies or data)).ti,ab.
161.	exp case control study/
162.	case control*.ti,ab.
163.	cross-sectional study/
164.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
165.	or/64-70,73-81
166.	exp "sensitivity and specificity"/
167.	(sensitivity or specificity).ti,ab.
168.	((pre test or pretest or post test) adj probability).ti,ab.
169.	(predictive value* or PPV or NPV).ti,ab.
170.	likelihood ratio*.ti,ab.
171.	((area under adj4 curve) or AUC).ti,ab.
172.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
173.	diagnostic accuracy/
174.	diagnostic test accuracy study/
175.	gold standard.ab.
176.	exp diagnostic error/
177.	(false positiv* or false negativ*).ti,ab.
178.	differential diagnosis/
179.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
180.	or/83-96
181.	42 and (52 or 63 or 82 or 97)

Cochrane Library (Wiley) search terms

#25.	MeSH descriptor: [Barrett Esophagus] explode all trees
#26.	barrett*:ti,ab
#27.	speciali* near/3 (epithel* or oesophag* or esophag* or mucos*):ti,ab
#28.	column* near/3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*):ti,ab

#29.	(intestin* near/2 metaplas*):ti,ab
#30.	(or #1-#5)
#31.	MeSH descriptor: [Precancerous Conditions] explode all trees
#32.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*):ti,ab
#33.	#7 or #8
#34.	MeSH descriptor: [Esophagus] explode all trees
#35.	MeSH descriptor: [Esophageal Mucosa] explode all trees
#36.	(oesophag* or esophag* or intramucosal* or intra-mucosal*):ti,ab
#37.	(or #10-#12)
#38.	#9 and #13
#39.	MeSH descriptor: [Esophageal Neoplasms] explode all trees
#40.	#6 or #14 or #15
#41.	MeSH descriptor: [Cytodiagnosis] this term only
#42.	((nonendoscop* or non endoscop* or minimal* invasive or noninvasive or non invasive or less invasive) near/3 (surveillanc* or approach* or screen* or monitor* or detect* or diagnos* or cytodiagnos* or cytolog* or assessment* or sampl* or collect* or brush* or biops* or examination* or test* or technique* or device* or tool* or capsule*)):ti,ab
#43.	((oesophag* or esophag* or cell*) near/3 (collect* or sampl* or device*)):ti,ab
#44.	(cytosponge* or esophacap* or esocheck* or aeonose* or balloon* or sponge* or (electronic nose)):ti,ab
#45.	(or #17-#20)
#46.	#16 and #21
#47.	conference:pt or (clinicaltrials or trialsearch):so
#48.	#22 not #23

Epistemonikos search terms

2.	(title:(Barrett* OR "oesophageal adenocarcinoma*" OR "esophageal adenocarcinoma*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "oesophageal carcinoma*" OR "esophageal carcinoma*" OR "oesophageal metaplas*" OR "esophageal dysplas*" OR "column* epithel*" OR "intestin* metaplas*" OR "intestin* dysplas*") OR abstract:(Barrett* OR "oesophageal adenocarcinoma*" OR "esophageal adenocarcinoma*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "oesophageal carcinoma*" OR "esophageal carcinoma*" OR "oesophageal metaplas*" OR "esophageal dysplas*" OR "column* epithel*" OR "intestin* metaplas*" OR "intestin* dysplas*")) AND (title:("non-endoscopic*" OR nonendoscopic* OR cytosponge* OR esophacap* OR esocheck* OR balloon OR sponge OR "cell collection sampling device*") OR abstract:("non-endoscopic*" OR nonendoscopic* OR cytosponge* OR esophacap* OR esocheck* OR balloon OR sponge OR "cell collection sampling device*")

G.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Barrett's Oesophagus population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health

Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 12: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 April 2022	
Embase (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 April 2022	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 April 2022	English language

Medline (Ovid) search terms

74.	exp Barrett esophagus/
75.	barrett*.ti,ab.
76.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
77.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
78.	or/1-4
79.	Precancerous conditions/
80.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or

	carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
81.	6 or 7
82.	exp Esophagus/
83.	Esophageal Mucosa/
84.	(oesophag* or esophag* or intramucosal* or intra-mucosal*).ti,ab.
85.	or/9-11
86.	8 and 12
87.	exp Esophageal Neoplasms/
88.	5 or 13 or 14
89.	letter/
90.	editorial/
91.	news/
92.	exp historical article/
93.	Anecdotes as Topic/
94.	comment/
95.	case report/
96.	(letter or comment*).ti.
97.	or/16-23
98.	randomized controlled trial/ or random*.ti,ab.
99.	24 not 25
100.	animals/ not humans/
101.	exp Animals, Laboratory/
102.	exp Animal Experimentation/
103.	exp Models, Animal/
104.	exp Rodentia/
105.	(rat or rats or mouse or mice or rodent*).ti.
106.	or/26-32
107.	15 not 33
108.	limit 34 to English language
109.	economics/
110.	value of life/
111.	exp "costs and cost analysis"/
112.	exp Economics, Hospital/
113.	exp Economics, medical/
114.	Economics, nursing/
115.	economics, pharmaceutical/
116.	exp "Fees and Charges"/
117.	exp budgets/
118.	budget*.ti,ab.
119.	cost*.ti.

120.	(economic* or pharmaco?economic*).ti.
121.	(price* or pricing*).ti,ab.
122.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
123.	(financ* or fee or fees).ti,ab.
124.	(value adj2 (money or monetary)).ti,ab.
125.	or/36-51
126.	quality-adjusted life years/
127.	sickness impact profile/
128.	(quality adj2 (wellbeing or well being)).ti,ab.
129.	sickness impact profile.ti,ab.
130.	disability adjusted life.ti,ab.
131.	(qal* or qtime* or qwb* or daly*).ti,ab.
132.	(euroqol* or eq5d* or eq 5*).ti,ab.
133.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
134.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
135.	(hui or hui1 or hui2 or hui3).ti,ab.
136.	(health* year* equivalent* or hye or hyes).ti,ab.
137.	discrete choice*.ti,ab.
138.	rosser.ti,ab.
139.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
140.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
141.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
142.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
143.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
144.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
145.	or/53-71
146.	35 and (52 or 72)

Embase (Ovid) search terms

72.	exp Barrett esophagus/
73.	barrett*.ti,ab.
74.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
75.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
76.	or/1-4
77.	Precancer/
78.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
79.	6 or 7
80.	exp Esophagus/

81.	Esophagus Mucosa/
82.	(oesophag* or esophag*).ti,ab.
83.	or/9-11
84.	8 and 12
85.	exp Esophagus Tumor/
86.	5 or 13 or 14
87.	letter.pt. or letter/
88.	note.pt.
89.	editorial.pt.
90.	case report/ or case study/
91.	(letter or comment*).ti.
92.	(conference abstract or conference paper).pt.
93.	or/16-21
94.	randomized controlled trial/ or random*.ti,ab.
95.	22 not 23
96.	animal/ not human/
97.	nonhuman/
98.	exp Animal Experiment/
99.	exp Experimental Animal/
100.	animal model/
101.	exp Rodent/
102.	(rat or rats or mouse or mice or rodent*).ti.
103.	or/24-31
104.	15 not 32
105.	limit 33 to English language
106.	health economics/
107.	exp economic evaluation/
108.	exp health care cost/
109.	exp fee/
110.	budget/
111.	funding/
112.	budget*.ti,ab.
113.	cost*.ti.
114.	(economic* or pharmaco?economic*).ti.
115.	(price* or pricing*).ti,ab.
116.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
117.	(financ* or fee or fees).ti,ab.
118.	(value adj2 (money or monetary)).ti,ab.
119.	or/35-47
120.	quality-adjusted life years/
121.	"quality of life index"/
122.	short form 12/ or short form 20/ or short form 36/ or short form 8/
123.	sickness impact profile/
124.	(quality adj2 (wellbeing or well being)).ti,ab.
125.	sickness impact profile.ti,ab.

126.	disability adjusted life.ti,ab.
127.	(qal* or qtime* or qwb* or daly*).ti,ab.
128.	(euroqol* or eq5d* or eq 5*).ti,ab.
129.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
130.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
131.	(hui or hui1 or hui2 or hui3).ti,ab.
132.	(health* year* equivalent* or hye or hyes).ti,ab.
133.	discrete choice*.ti,ab.
134.	rosser.ti,ab.
135.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
136.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
137.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
138.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
139.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
140.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
141.	or/49-69
142.	34 and (48 or 70)

NHS EED and HTA (CRD) search terms

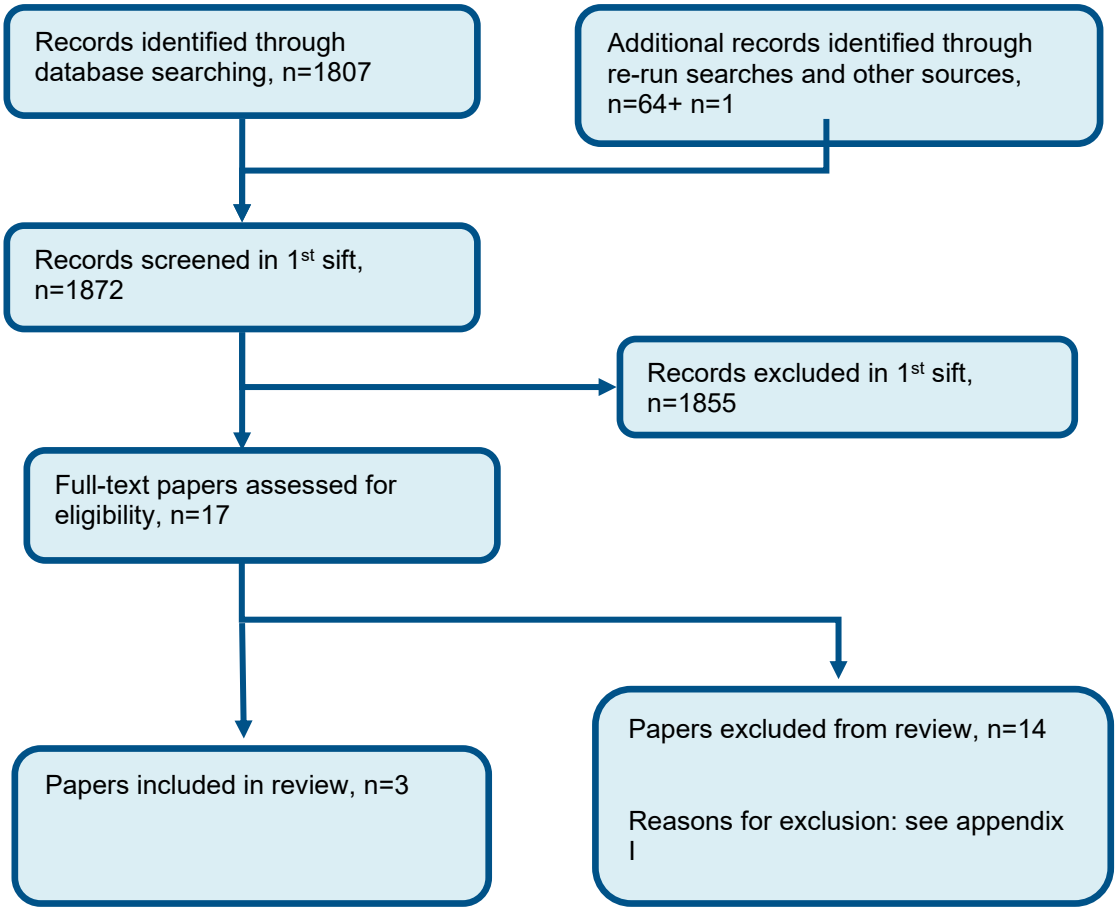
#17.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#18.	(barrett*)
#19.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)
#20.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#21.	#1 OR #2 OR #3 OR #4
#22.	MeSH DESCRIPTOR Precancerous Conditions EXPLODE ALL TREES
#23.	((dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma*or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*))
#24.	#6 OR #7
#25.	MeSH DESCRIPTOR Esophagus EXPLODE ALL TREES
#26.	MeSH DESCRIPTOR Esophageal Mucosa EXPLODE ALL TREES
#27.	(oesophag* or esophag* or intramucosal* or intra-mucosal*)
#28.	#9 OR #10 OR #11
#29.	#8 AND #12
#30.	#5 OR #13
#31.	MeSH DESCRIPTOR Esophageal Neoplasms EXPLODE ALL TREES
#32.	#14 OR #15

INAHTA search terms

1.	("Barrett Esophagus"[mh]) OR (Barrett*) OR (Esophageal Neoplasms)[mh]

Appendix H –Diagnostic evidence study selection

Figure 2: Flow chart of clinical study selection for the review of diagnostic accuracy of non-endoscopic surveillance techniques



Appendix I – Diagnostic evidence

Reference	**Falk 1997** [1]
Study type	Prospective cohort study
Study methodology	Data source: patients undergoing surveillance endoscopy for Barrett's oesophagus or referred for further management of dysplasia from March 1994 to November 1995 Recruitment: consecutive
Number of patients	n = 63
Patient characteristics	Age, mean (range): 61.3 (29-81) years Gender (male to female ratio): 55/8 Ethnicity: not specified Setting: not specified Country: USA Characteristics: mean (SD) length of Barrett's epithelium was 5.6 (3.6) cm with range of 1-15 cm; short-segment Barrett's oesophagus was found in 12 patients; endoscopic abnormalities encountered in the Barrett's epithelium included ulcers (5 patients), nodularity (3 patients and plaques (2 patients). Inclusion criteria: patients undergoing surveillance endoscopy for Barrett's oesophagus or referred for further management of dysplasia from March 1994 to November 1995. Exclusion criteria: No patient had endoscopic evidence of carcinoma or was referred for the evaluation of new-onset dysphagia.
Target condition	High grade dysplasia or adenocarcinoma

Reference	**Falk 1997** [1]				
Index test(s) and reference standard	Index test: Balloon cytology Non-endoscopic cytological specimens were obtained with a Brandt oesophageal cytology balloon (diameter 30mm when inflated with 20mL of air and 9mm when deflated). Soft cones on the balloon enhance cell collection. Reference standard: Histology (after endoscopic biopsy and brush cytology) Endoscopy was performed with the Olympus GIF-1T100 or GIF-2T100 videoendoscope (Olympus Corp., Melville NY). Endoscopically directed brush cytology specimens were obtained with the Bard cytology brush (C.R. Bard Inc., Tewksbury, MA) from all four quadrants of the Barrett's segment as well as from endoscopically noted abnormalities such as ulcers, nodules or plaques. After brush cytology, endoscopic surveillance biopsies were performed using a standard protocol (the University of Washington protocol). Biopsy specimens were obtained with the 'jumbo' spiked-biopsy forceps (Olympus FB-13K) from four quadrants at 2cm intervals along the entire length of Barrett's epithelium. Histology: Biopsy specimens were fixed in Hollande's solution and a minimum of four step-sections were stained. The type of columnar epithelium was noted with special attention given to the presence or absence of specialized columnar epithelium. Dysplasia was diagnosed using an established classification scheme: 1) negative for dysplasia, 2) low-grade or indefinite dysplasia, 3) high-grade dysplasia and 4) intramucosal or submucosal carcinoma. All slides were interpreted by a single pathologist who had no knowledge of the cytology findings. All specimens of dysplasia and cancer were analysed subsequently by a second pathologist who also was blinded to the cytology findings and the histological interpretation of the first pathologist. Time between measurement of index test and reference standard: not specified				
2×2 table		Reference standard +	Reference standard −	Total	**2x2 table for detecting high-grade dysplasia/ adenocarcinoma** (low-grade or indefinite for dysplasia grouped with normal histology) Columnar epithelium was obtained in 52 patients, used in the present analysis.
	Index test +	8	2	10	
	Index test −	2	40	42	
	Total	10	42	52	
2x2 table		Reference standard +	Reference standard −	Total	**2x2 table for detecting adenocarcinoma**; calculated excluding those with HGD, LGD or indefinite for dysplasia
	Index test +	6	0	6	
	Index test −	2	34	36	
	Total	8	34	42	
2x2 table		Reference standard +	Reference standard −	Total	**2x2 table for detecting high-grade dysplasia**; calculated excluding those with adenocarcinoma, LGD or indefinite for dysplasia
	Index test +	2	0	2	
	Index test −	0	34	34	
	Total	2	34	36	

Reference	**Falk 1997** [1]				
2x2 table		Reference standard +	Reference standard −	Total	**2x2 table for detecting low-grade or indefinite for dysplasia**; calculated excluding those with HGD or cancer
	Index test +	2	0	2	
	Index test −	6	34	40	
	Total	8	34	42	
2x2 table		Reference standard +	Reference standard −	Total	2x2 table for detecting abnormal histological results (**all levels of dysplasia or carcinoma**) compared with normal cytology
	Index test +	10	0	10	
	Index test −	8	34	42	
	Total	18	34	52	
Statistical measures	Index text: Balloon cytology 1) For detecting **high-grade dysplasia/ adenocarcinoma** (low-grade or indefinite for dysplasia grouped with normal histology) Sensitivity: 0.80 (95% CI 0.44-0.97) Specificity: 0.95 (95% CI 0.84-0.99) 2) For detecting **adenocarcinoma** (excluding those with HGD, LGD or indefinite for dysplasia) Sensitivity: 0.75 (95% CI 0.35-0.97) Specificity: 1.00 (95% CI 0.90-1.00) 3) For detecting **high-grade dysplasia** (excluding those with adenocarcinoma, LGD or indefinite for dysplasia) Sensitivity: 1.00 (95% CI 0.16- 1.00) Specificity: 1.00 (95% CI 0.90-1.00) 4) For **detecting low-grade or indefinite for dysplasia** (excluding HGD/adenocarcinoma) Sensitivity: 0.25 (95% CI 0.03- 0.65) Specificity: 1.00 (95% CI 0.90- 1.00) **5)** For detecting **any level of dysplasia or carcinoma** Sensitivity: 0.56 (95% CI 0.31- 0.78) Specificity: 1.00 (95% CI 0.90-1.00)				
Source of funding	Not specified				

Reference	**Falk 1997** [1]
Limitations	Risk of bias: no serious risk of bias Indirectness: no concerns
Comments	

Reference	**Katz 2017**[2]
Study type	Retrospective case control
Study methodology	Data source: Patients known to have dysplasia and patients with non-dysplastic Barrett's oesophagus from BEST2 and Case 1 trials Recruitment: not specified
Number of patients	n = 31 patients with non-dysplastic Barrett's; n=28 patients with known dysplasia
Patient characteristics	Age, median (range): non dysplastic 64 (16-81); dysplastic 66.5 (51-81) Gender (male to female ratio): 3.4:1 for non-dysplastic; 8.3:1 for dysplastic sample Ethnicity: not specified Setting: University of Cambridge, Biomedical Campus Country: UK Inclusion criteria: clear dysplasia status and sufficient remaining tissue (>5 gland groups) which passed sequencing quality control; Barrett's oesophagus of any length provided that it was TFF3 positive. Exclusion criteria: no surveillance endoscopy with biopsies performed on the same day, with available pathology; TFF3 negative, <5 gland groups, uncertain dysplasia status <u>Characteristics</u> Non-dysplastic: median (range) circumferential length of Barrett's (cm): 1 (0-10); median (range) maximum length of Barrett's (cm): 4 (1-11)

Reference	**Katz 2017[2]**				
	Dysplastic: median (range) circumferential length of Barrett's (cm): 4 (0-16); median (range) maximum length of Barrett's (cm): 6 (0-17); n=10 had low-grade dysplasia, n=6 had high grade dysplasia, n=12 intramucosal carcinoma samples				
Target condition	Dysplasia				
Index test(s) and reference standard	Index test: Cytosponge (using the Ion AmpliSeq Cancer Hotspot panel V2 to detect mutations) All samples had been processed into paraffin blocks. The 10 x 4 µm sections of Cytosponge tissue were cut on to unchanged slides with an H&E at each end. Areas of atypia were marked by a specialist pathologist and dissected with additional glands taken to give an adequate DNA yield and the estimated % atypia was recorded. For samples with no atypia either all glands were dissected if they were few or a selection of glands from each quadrant was sampled if Barrett's tissue was prominent throughout the sections. An in-house clinically validated protocol was used for DNA extraction. Quantification was performed using the Qubit High Sensitivity assay on the Qubit 2.0 fluorometer as per the manufacturer's instructions. Amplicon library preparation was performed using the Ion AmpliSeq Library Kit 2.0 with target region amplification, amplicon partial digestion with FuPa reagent, barcode adapter ligation and library purification. Libraries were quantified using the Qubit 2.0 fluorometer or using Agilent 4200 TapeStation System. Sequencing was performed on the Ion Torrent PGM platform. Sixteen samples were loaded per chip to give an average of 1000x coverage per amplicon. TP53 coverage was used for quality control and samples with coverage <100x for each exon were considered to have failed. This reflected the coverage of all mutations. Mutation analysis: sequences were aligned to the human hg19 reference genome and mutation calling was performed by the Ion Torrent Suite Version 5.2. Each non-synonymous variant call was then visually inspected in the BAM file using the Integrated Genome Viewer version 2.3.59. Common single nucleotide polymorphisms (SNV) were excluded from further analysis, if present at either 50% or 100% of the sample, indicating them to have been inherited as were known false positives caused by non-specific primer binding. Where there was sufficient material, samples were run in duplicate with repeat library preparation and SNV calls were made when the mutation was seen in both runs. If cases had an allele frequency (AF) ≥12%, >7 base paires from the amplicon edge and with no strand bias >3.0 x then these were sufficient to call without performing a duplicate. Reference standard: Surveillance endoscopy with biopsies Biopsies from endoscopies were reviewed in consensus meetings by 2-4 expert pathologists, blinded to the Cytosponge result. If a patient had undergone an endoscopy within 6 months prior to Cytosponge and was found to have a higher grade at that timepoint without subsequent therapy, this grade was assigned with the assumption that the lesion had not been samples on the subsequent occasion. Time between measurement of index test and reference standard: same day				
2×2 table		Reference standard +	Reference standard −	Total	Results for detecting dysplasia (any) vs no dysplasia based on detection of mutated cases on the cytosponge.
	Index test +	20	3	23	
	Index test −	8	28	36	

Reference	**Katz 2017[2]**				
	Total	28	31	59	
Statistical measures	Index text: cytosponge Sensitivity: 0.71 (95% CI 0.51 – 0.87) Specificity: 0.90 (95% CI 0.74 – 0.98)				
Source of funding	Human Research Tissue Bank (supported by the NIHR); Cancer research UK; the Medical Research Council				
Limitations	Risk of bias: serious concerns due unclear participant recruitment method Indirectness: no concerns				
Comments					

Reference	**Pilonis 2022 [4]**
Study type	Retrospective multi-centre cross-sectional study (including a real-life prospective cohort; data not yet published)
Study methodology	Data source: Patients who had received cytosponge and confirmatory endoscopy during the BEST2 and BEST3 trials from July 2011 to April 2019; Patients who had their Barrett's oesophagus surveillance delayed due to decreased endoscopy provision during the COVID-19 pandemic (DELTA implementation study). Recruitment: consecutive
Number of patients	Training cohort: n = 557; validation cohort: n=334; real world prospective cohort: n=223 (endoscopic data still being collected; not published)
Patient characteristics	Age, mean (range): training cohort 65 (59-72); validation cohort 67 (58-73); prospective cohort 69 (60-74) Gender (male to female ratio): training cohort 453/104; validation cohort 250/84; prospective cohort 165/58 Ethnicity: n=545 white, n=11 other, n=1 missing for training cohort; ethnicity for the other cohorts was not specified. Setting: Hospitals across England; Tertiary referral centre; four community hospitals Country: UK

Reference	Pilonis 2022 [4]
	Inclusion criteria: Patients with confirmed diagnosis of Barrett's oesophagus who had received cytosponge and confirmatory endoscopy >18 years who were having endoscopic surveillance for Barrett's oesophagus as part of the BEST2 and BEST3 trials; > (with intestinal metaplasia confirmed by TFF3 and a minimum Barrett's segment length of 1cm) Characteristics (median (IQR)): Barrett's oesophagus maximum segment length (cm): training cohort 5 (3-8); validation cohort 3 (2-6); prospective cohort 3 (2-6) Barrett's oesophagus circumferential length (cm): training cohort 3 (1-6); validation cohort 1 (0-4); prospective cohort 1 (0-4) Body-mass index kg/m^2 : training cohort 28.25 (25.61-31.07); validation cohort 27.90 (25.20-30.81); prospective cohort 26.90 (24.12-29.30)
Target condition(s)	High-grade dysplasia or cancer; Any grade of dysplasia (LGD, HGD or cancer)
Index test(s) and reference standard	Index test: Cytosponge Cytosponge (Europlaz, Southminster, UK for BEST2 and BEST 3; Medronic, Minneapolis, MN,USA for DELTA) was administered by clinical nurses in DELTA and a research nurse in BEST2 and BEST3. Atypia and p53 immunochemistry were performed on formalin-fixed paraffin-embedded slides from the Cytosponge. Atypia was assessed on the haematoxylin and eosin slide and included both clear dysplasia and atypia of unknown significance. A p53 immunohistochemistry staining with an intensity of 3 was considered significant as previously published. The p53 absent staining pattern cannot be reliably ascertained from cytosponge samples so these cases could be missed. Both biomarker tests were considered positive if there was a consensus diagnosis from at least two expert pathologists, and in some cases evaluation of the p53 alongside the haematoxylin and eosin could help to clarify the atypia diagnosis. Primary outcome was a diagnosis of high-grade dysplasia or cancer detected in any of the endoscopic biopsies. For invasive cancer cases, the degree of invasion was determined from the endoscopic mucosal resection and intramucosal cancer was used to denote cases confined to the mucosal layer (T1a) at the procedure following the Cytosponge test. **The objective was to identify a high-risk group for the primary outcomes using any combination of Cytosponge and clinical variables.** Secondary outcome was diagnosis of any grade of dysplasia (LGD, HGD, cancer); indefinite for dysplasia was not considered abnormal due to the subjectivity of the assessment and poor intra-observer agreement. Biomarkers (atypia and p53 overexpression immunohistochemistry) and significant clinical demographic variables identified in logistic regression models were used to generate a simple decision tree using R version 3.6.2. **The highest risk group** was comprised of biomarker-positive cases, as these identified the greatest proportion of both primary and secondary outcomes in patients. **The moderate risk group** was selected to minimise false-negative results.

Reference	**Pilonis 2022** [4]				
	For those patients with no atypia or p53 overexpression on their Cytosponge, clinical risk factors (ultra-long Barrett's oesophagus or long segment, male sex or age older than 60 years) associated with primary and secondary outcomes were used to identify patients at risk, and cut-offs were derived to maximise sensitivity at the expense of specificity. **Sensitivity** for identification of dysplasia was evaluated using AUROC for all high-risk and moderate-risk patients versus low-risk patients. <u>Reference standard: Endoscopy</u> Endoscopies were performed by the local gastroenterologist on the same day as Cytosponge (BEST2) or within 2 months of Cytosponge (BEST 3). Time between measurement of index test and reference standard: same day or within 2 months. **For the purpose of the present review, results based on Cytosponge 'biomarker-positive only' for the combined cohorts have been extracted and used to calculate Sensitivity and Specificity as out of all analyses presented in the paper, it most closely matched the protocol and what is done in current practice; analyses based on cytosponge biomarker-positive plus clinical risk factors or clinical risk factors only have not been extracted.**				
2x2 table		Reference standard +	Reference standard −	Total	**High-grade dysplasia or cancer in the Training cohort;** 2x2 calculated using: 'p53 overexpression and atypia', 'p53 overexpression only' and 'atypia only' as identified in the Cytosponge as positive cases and 'neither' as negative cases
	Index test +	68	64	132	
	Index test −	24	401	425	
	Total	92	465	557	
		Reference standard +	Reference standard −	Total	**High-grade dysplasia or cancer in the Validation cohort;** 2x2 calculated using: 'p53 overexpression and atypia', 'p53 overexpression only' and 'atypia only' as identified in the Cytosponge as positive cases and 'neither' as negative cases; Pathology results missing for 1 patient, hence total n=343
	Index test +	31	48	79	
	Index test −	4	260	264	
	Total	35	308	343	
		Reference standard +	Reference standard −	Total	**Any grade of dysplasia or cancer in the Training cohort**
	Index test +	87	45	132	
	Index test −	47	378	425	
	Total	134	423	557	
		Reference standard +	Reference standard −	Total	**Any grade of dysplasia or cancer in the Validation cohort**
	Index test +	46	33	79	

Reference	**Pilonis 2022** [4]				
	Index test −	18	246	264	
	Total	64	279	343	
2x2 table		Reference standard +	Reference standard −	Total	
	Index test +	99	112	211	
	Index test −	28	661	689	
	Total	127	773	900	
		Reference standard +	Reference standard −	Total	
	Index test +	133	78	211	
	Index test −	65	624	689	
	Total		702	900	
Statistical measures	Index test Cytosponge (biomarker-positive only); outcome: high-grade dysplasia or cancer in the training cohort Sensitivity: 0.74 (95% CI 0.64-0.83) Specificity: 0.86 (95% CI 0.83- 0.89) Index test Cytosponge (biomarker-positive only); outcome: high-grade dysplasia or cancer in the validation cohort Sensitivity: 0.89 (95% CI 0.73-0.97) Specificity: 0.84 (95% 0.80-0.88) Index test Cytosponge (biomarker-positive only); outcome: any grade of dysplasia or cancer in the training cohort Sensitivity: 0.65 (95% CI 0.56-0.73) Specificity: 0.89 (95% CI 0.86- 0.92) Index test Cytosponge (biomarker-positive only); outcome: any grade of dysplasia or cancer in the validation cohort Sensitivity: 0.72 (95% CI 0.59-0.82) Specificity: 0.88 (95% 0.84-0.92)				
Source of funding	Partly funded by: Medical Research council, Innovate UK (DELTA study), Cancer Research UK (BEST 2 and BEST 3 studies), pre-doctoral bursary from Cancer Research UK.				
Limitations	Risk of bias: no serious risk of bias Indirectness: no concerns				

Reference	**Pilonis 2022** [4]
Comments	

Appendix J – Forest plots

Coupled sensitivity and specificity forest plots

Figure 3: FFPE Cytosponge for dysplasia (ref. standard: surveillance endoscopy with biopsy)

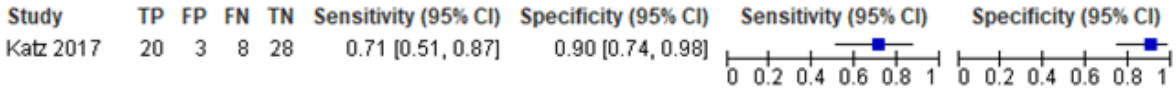


Figure 4: Cytosponge (biomarker positive) to detect high-grade dysplasia/cancer (ref. standard: endoscopy)

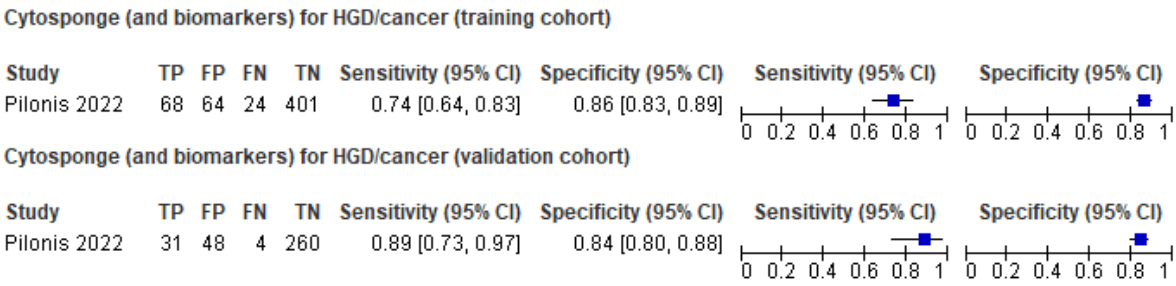


Figure 5: Cytosponge (biomarker positive) to detect any grade of dysplasia/cancer (ref. standard: endoscopy)

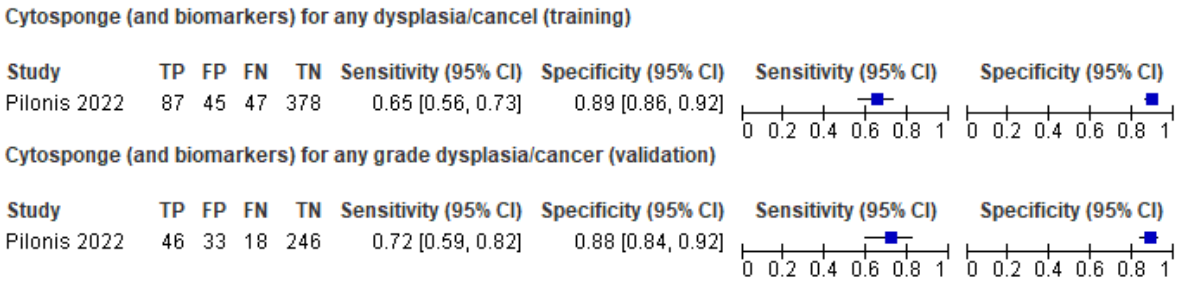


Figure 6: Balloon cytology to detect high-grade dysplasia/adenocarcinoma (ref. standard: histology after cytological brushing)

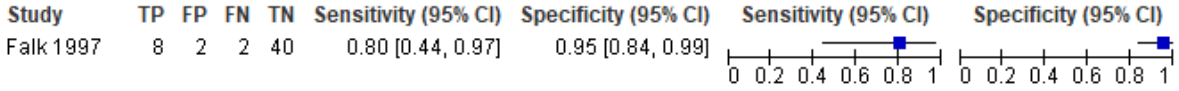
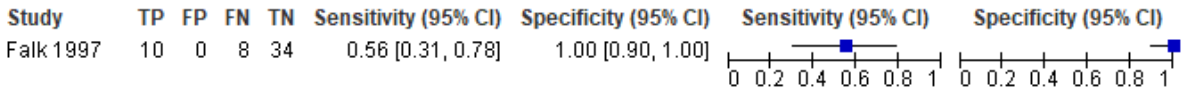
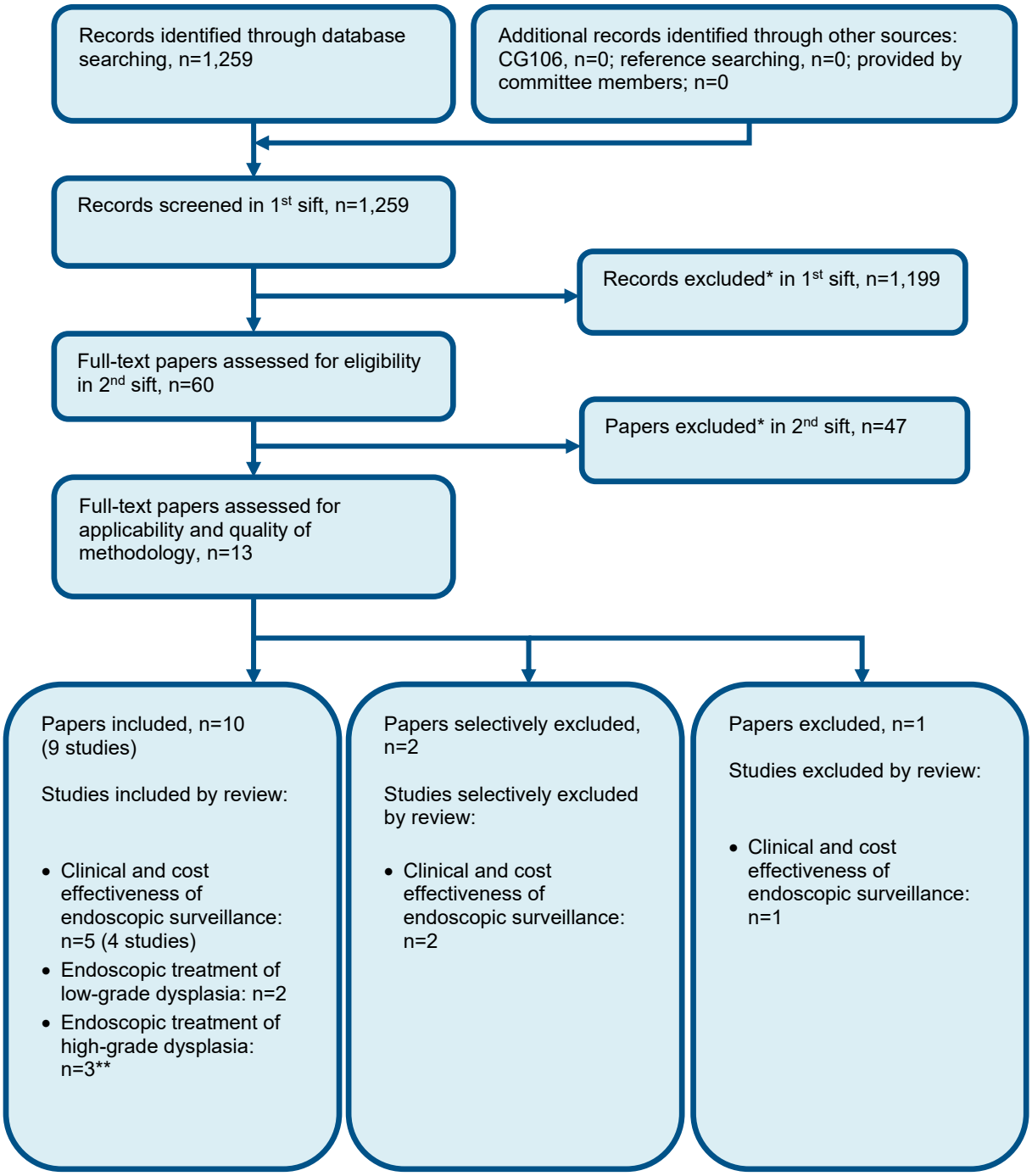


Figure 7: Balloon cytology to detect any level of dysplasia/adenocarcinoma (ref. standard: histology after cytological brushing)



Appendix K – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
** One article identified was applicable to endoscopic treatment of low-grade dysplasia and endoscopic treatment for high-grade dysplasia, for the purposes of this diagram they have been included under endoscopic treatment of low-grade dysplasia only.

Appendix L – Excluded studies

Clinical studies

Table 13: Studies excluded from the clinical review

Study	Reason for exclusion
Chanvitan, A., Geater, A. F., Ubolcholket, S. et al. (1990) Early detection of oesophageal carcinoma in southern Thailand. Journal of the Medical Association of Thailand 73(10): 565-71	- Population not relevant to this review protocol *not non-dysplastic Barrett's; includes people that were symptomatic of oesophageal cancer*
Chavalitdhamrong, D., Chen, G. C., Roth, B. E. et al. (2011) Esophageal capsule endoscopy for evaluation of patients with chronic gastroesophageal reflux symptoms: findings and its image quality. Diseases of the Esophagus 24(5): 295-8	- Population not relevant to this review protocol *reflux disease and suspected Barrett's oesophagus; no relevant outcomes*
Dawsey, S. M., Shen, Q., Nieberg, R. K. et al. (1997) Studies of esophageal balloon cytology in Linxian, China. Cancer Epidemiology, Biomarkers & Prevention 6(2): 121-30	- Review article but not a systematic review *studies analysis was based did not meet protocol*
Duvvuri, A., Desai, M., Vennelaganti, S. et al. (2021) Diagnostic accuracy of a novel third generation esophageal capsule as a non-invasive detection method for Barrett's esophagus: A pilot study. Journal of Gastroenterology and Hepatology (Australia) 36(5): 1222-1225	- No relevant outcomes *detection of Barrett's oesophagus*
Fitzgerald, R. C., di Pietro, M., O'Donovan, M. et al. (2020) Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial. Lancet 396(10247): 333-344	- Population not relevant to this review protocol *excluded patients with confirmed diagnosis of Barrett's oesophagus; no relevant outcomes*
Haisley, K. R., Dolan, J. P., Olson, S. B. et al. (2017) Sponge Sampling with Fluorescent In Situ Hybridization as a Screening Tool for the Early Detection of Esophageal Cancer. Journal of Gastrointestinal Surgery 21(2): 215-221	- Population not relevant to this review protocol *Includes people with a history of gastroesophageal reflux disease, 10 of which had dysplasia at baseline, 19 had normal findings and only 20 had metaplasia (i.e. non-dysplastic Barrett's oesophagus)*
Kadri, S. R., Lao-Sirieix, P., O'Donovan, M. et al. (2010) Acceptability and accuracy of a non-endoscopic screening test for Barrett's	- No relevant outcomes

Study	Reason for exclusion
oesophagus in primary care: cohort study. BMJ 341: c4372	*diagnosis of Barrett's oesophagus; population did not have confirmed Barrett's at the time of testing.*
Lao-Sirieix, P., Boussioutas, A., Kadri, S. R. et al. (2009) Non-endoscopic screening biomarkers for Barrett's oesophagus: From microarray analysis to the clinic. Gut 58(11): 1451-1459	- Population not relevant to this review protocol *the majority were healthy controls without Barrett's oesophagus; no relevant outcomes*
Moinova, H. R., LaFramboise, T., Lutterbaugh, J. D. et al. (2018) Identifying DNA methylation biomarkers for non-endoscopic detection of Barrett's esophagus. Science Translational Medicine 10(424)	- Population not relevant to this review protocol
Paterson, A. L., Gehrung, M., Fitzgerald, R. C. et al. (2020) Role of TFF3 as an adjunct in the diagnosis of Barrett's esophagus using a minimally invasive esophageal sampling device-The CytospongeTM. Diagnostic Cytopathology 48(3): 253-264	- Review article but not a systematic review
Ross-Innes, C. S., Debiram-Beecham, I., O'Donovan, M. et al. (2015) Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multi-center case-control study. PLoS Medicine / Public Library of Science 12(1): e1001780	- Population not relevant to this review protocol *; incorrect population and outcome: the study looks at diagnostic accuracy of cytosponge in detecting Barrett's oesophagus in a cohort of people with Barrett's and controls with dyspepsia but without Barrett's.*
Shaheen, N. J., Komanduri, S., Muthusamy, V. R. et al. (2022) Acceptability and Adequacy of a Non-endoscopic Cell Collection Device for Diagnosis of Barrett's Esophagus: Lessons Learned. Digestive Diseases & Sciences 67(1): 177-186	- Population not relevant to this review protocol *mixed sample of Barrett's oesophagus and GERD patients; no relevant outcomes: diagnosis of Barrett's oesophagus but not dysplasia*
Sharma, P., Wani, S., Rastogi, A. et al. (2008) The diagnostic accuracy of esophageal capsule endoscopy in patients with gastroesophageal reflux disease and Barrett's esophagus: a blinded, prospective study. American Journal of Gastroenterology 103(3): 525-32	- No relevant outcomes *diagnostic accuracy for detecting Barrett's oesophagus*
Zhou, Z., Kalatskaya, I., Russell, D. et al. (2019) Combined EsophaCap cytology and MUC2 immunohistochemistry for screening of intestinal	- Population not relevant to this review protocol *included patients with previously documented gastroesophageal reflux disease, Barrett's*

Study	Reason for exclusion
metaplasia, dysplasia and carcinoma. Clinical & Experimental Gastroenterology 12: 219-229	*oesophagus, low- or high-grade dysplasia, squamous cell carcinoma.*

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.