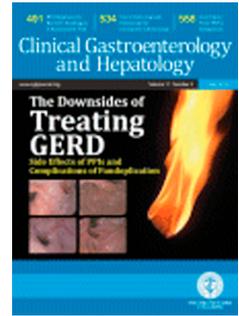


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# Acceptability, Accuracy and Safety of Disposable Transnasal Capsule Endoscopy for Barrett's Esophagus Screening

## Short title:

Transnasal capsule for Barrett's screening.

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**Abbreviations:**

AUROC Area under the receiver operating characteristic

BE Barrett's Esophagus

C-EGD Conventional esophagogastroduodenoscopy

CI Confidence interval

EAC Esophageal adenocarcinoma

IQR interquartile range

LSBE Long segment Barrett's esophagus

SD Standard deviation

SEM Standard error of the mean

SSBE Short segment Barrett's esophagus

STAI-6 Spielberger State Trait Anxiety Inventory

TNE Transnasal endoscopy

VAS visual analogue scale

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Sarmed S. Sami contributed to the conception and design of the study; acquisition of data; analysis; interpretation of data; and drafted the manuscript.

Prasad G. Iyer contributed to the conception and design of the study; acquisition of data; analysis; interpretation of data; and critical revision of the manuscript for important intellectual content.

Pratchi Pophali contributed to the acquisition of data; analysis; interpretation of data; and critical revision of the manuscript for important intellectual content.

Magnus Halland contributed to the acquisition of data and critical revision of the manuscript for important intellectual content.

Massimiliano di Pietro contributed to the acquisition of data and critical revision of the manuscript for important intellectual content.

Jacobo Ortiz-Fernandez-Sordo contributed to the acquisition of data and critical revision of the manuscript for important intellectual content.

Jonathan R. White contributed to the acquisition of data and critical revision of the manuscript for important intellectual content.

Michele Johnson contributed to the acquisition of data and critical revision of the manuscript for important intellectual content.

Indra Neil Guha contributed to the conception and design of the study and critical revision of the manuscript for important intellectual content.

Rebecca C. Fitzgerald contributed to the conception and design of the study and critical revision of the manuscript for important intellectual content.

Krish Rangunath contributed to the conception and design of the study; acquisition of data; interpretation of data; and critical revision of the manuscript for important intellectual content.

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## ABSTRACT

**Background & Aims:** Screening for Barrett's esophagus (BE) with conventional esophagogastroduodenoscopy (C-EGD) is expensive. We assessed the performance of a clinic-based, single use transnasal capsule endoscope (EG Scan II) for the detection of BE, compared to C-EGD as the reference standard.

**Methods:** We performed a prospective multicenter cohort study of patients with and without BE recruited from 3 referral centers (1 in the United States and 2 in the United Kingdom). Of 200 consenting participants, 178 (89%) completed both procedures (11% failed EG Scan due to the inability to intubate the nasopharynx). The mean age of participants was 57.9 years and 67% were male. The prevalence of BE was 53%. All subjects underwent the 2 procedures on the same day, performed by blinded endoscopists. Patients completed preference and validated tolerability (10-point visual analogue scale [VAS]) questionnaires within 14 days of the procedures.

**Results:** A higher proportion of patients preferred the EG Scan (54.2%) vs the C-EGD (16.7%) ( $P<.001$ ) and the EG Scan had a higher VAS score (7.2) vs the C-EGD (6.4) ( $P=.0004$ ). No serious adverse events occurred. The EG Scan identified any length BE with a sensitivity value of 0.90 (95% CI, 0.83–0.96) and a specificity value of 0.91 (95% CI, 0.82–0.96). The EG Scan identified long segment BE with a sensitivity value of 0.95 and short segment BE with a sensitivity values of 0.87.

**Conclusion:** In a prospective study, we found the EG Scan to be safe and to detect BE with higher than 90% sensitivity and specificity. A higher proportion of patients preferred the EG Scan to C-EGD. This device might be used as a clinic-based tool to screen populations at risk for BE. ISRCTN registry identifier: 70595405; ClinicalTrials.gov no: NCT02066233.

**KEY WORDS:** Esophageal adenocarcinoma; portable; imaging; reflux; office

## INTRODUCTION

Recent society guidelines have provided more support to screening individuals with multiple risk factors for Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC), such as chronic reflux symptoms, central obesity and a family history of EAC or BE<sup>1, 2</sup>, though the number of risk factors which may trigger a decision to screen and, more importantly, the tools to screen remain unclear.

While conventional esophagogastroduodenoscopy (C-EGD) remains the reference standard test to diagnose BE, it is not suitable for wide spread screening due to direct and indirect costs associated with sedation, recovery and monitoring<sup>3</sup>. The technical success rate of unsedated transnasal endoscopy (TNE) is comparable to C-EGD and the former was more preferred by patients<sup>4</sup>. However, the conventional TNE devices still require dedicated endoscopy suites with specialized equipment and decontamination facilities, hence, they have limited potential for widespread use in population screening<sup>5</sup>. Recent reports have demonstrated the acceptability, safety and accuracy of modified endoscopic transnasal techniques (EndoSheath<sup>®</sup>)<sup>6, 7</sup> in screening for BE. The EndoSheath<sup>®</sup> transnasal esophagoscope is portable and utilizes a disposable sheath with a biopsy channel that covers the endoscope to reduce the risk of cross contamination, but it still requires cleaning of the scope with alcohol wipe and an enzymatic detergent after every use.

The EG Scan<sup>™</sup> II (second generation) transnasal video esophagoscope (Intromedic Ltd., Seoul, South Korea) incorporates a disposable probe which omits the need for reprocessing. Moreover, it is highly compact and portable therefore can be used in the clinic or any other setting with rapid turnaround of patients. The aim of the current study was to assess the

technical feasibility, quality, safety, acceptability and accuracy of clinic-based TNE using the EG Scan compared to C-EGD as the reference standard.

## **MATERIALS AND METHODS**

### **Study design and settings**

This was a prospective diagnostic cohort study performed in three tertiary referral centers, 2 in the UK (Nottingham and Cambridge University Hospitals) and 1 in the USA (Mayo Clinic, Rochester, MN). All procedures were performed between July 2012 and October 2015 and all participants provided written informed consent. The trial received approval from the East Midlands research ethics committee (UK) and from the Mayo Clinic (Rochester, USA) Institutional Review Boards. It was prospectively registered (ISRCTN registry identifier: 70595405; ClinicalTrials.gov identifier: NCT02066233). The research was conducted and reported according to the standards for the reporting of diagnostic accuracy studies (STARD) statement<sup>8</sup>. All authors had access to the study data and reviewed and approved the final manuscript.

### **Participants**

Consecutive adult patients referred for clinical C-EGD with and without histologically confirmed BE of any length were invited to participate. BE patients were undergoing clinically indicated endoscopy for surveillance or therapy of BE related neoplasia. Patients without known BE were undergoing endoscopy for other clinical indications which included dyspepsia, heartburn, dysphagia and nausea/vomiting. Exclusion criteria were recurrent epistaxis (more than once a week); complete nasal obstruction; diseases of the nasal cavity; and anticoagulant use. All eligible patients were identified from the endoscopy referral database and approached by the study coordinators either via a letter or phone call to inform them of study details. Subjects were asked to express their interest in taking part or not

either at the time of the phone call or by returning a pre-paid self-addressed reply envelope to the study coordinators.

### **Interventions**

All patients underwent TNE first using the EG Scan (index test) followed by C-EGD (reference standard) on the same day by two different operators who were blinded to the findings of each other. TNE procedures were performed by certified endoscopists (S.S.S. in Nottingham; M.D.P. in Cambridge; P.G.I. and M.H. at Mayo Clinic) who had limited prior experience in using the EG Scan device (performed 1-3 procedures in the past), but had performed over 1000 C-EGD procedures. P.G.I also had experience in performing TNE (n=200).

At both procedures, a note was made of any suspected BE and the segment length was defined using the Prague criteria <sup>9</sup>. Demographic and procedure data were collected and patients were asked to fill in validated questionnaires within 14 days after the procedures.

### **The EG Scan™ II system**

The second generation EG Scan system (Figure 1) components are described in supplementary Table 1.

### **Endoscopy procedures**

The EG Scan procedure was performed in an outpatient clinic room with the patient sitting in a chair next to the physician's desk. Prior to commencing the procedure, participants were given a 100-ml liquid oral drink which is a mixture of water; orange cordial flavoring; a mucolytic (10 mls of 200 mg/ml N-acetylcysteine); and an anti-foaming agent (1ml of Simeticone 40 mg/ml) in order to improve visualization of the mucosa (UK centers only). A topical aerosol spray (Lidocaine Hydrochloride 5% and Phenylephrine Hydrochloride 0.5%) was applied to the patient's nares (3-4 sprays) 3-5 minutes prior to the procedure. The probe was introduced into the right or left nares and advanced into the proximal esophagus under

direct vision. The operator inspected the esophagus and the gastro-esophageal junction (indicated by the top of the proximal gastric folds) both in forward and retro-flexion views. Following the procedure, the probe was disconnected from the hand-held controller and discarded. The system was dismantled and stored in the accompanying suitcase (figure 1A).

The C-EGD procedures were performed in the endoscopy suite using a 9.8-mm diameter high definition endoscope (GIF-260H, Olympus Keymed, Essex, UK or GIF-H180, Olympus America, Center Valley, PA). Patients in the UK centers were offered either a topical anesthetic spray (applied to the posterior pharynx, 5-10 sprays, Lidocaine 10mg/dose, Xylocaine, AstraZeneca, Luton, UK) or conscious sedation (intravenous midazolam with or without pethidine or fentanyl) for their C-EGD procedures, while all the USA participants received conscious sedation.

### **Patient questionnaires**

All post-procedure questionnaires were administered by the study coordinators and completed by patients with the endoscopists blinded. Patients' tolerability was measured using a validated 10-point visual analogue scale (VAS)<sup>10</sup>. Patients were asked to describe their overall experience of both procedures by placing a cross on a line from "0" (worst ever experience) to "10" (best ever experience). Patients were asked which procedure they would prefer to have in the future if clinically indicated (EG Scan, or C-EGD, or either)). Tolerability and preference questionnaires were completed using prepaid self-addressed return envelopes at least 24 hours after procedures to allow for the complete resolution of sedation effects. We also measured the degree of gagging, choking, discomfort, and nasal pain immediately after EG Scan using the same scale where "0" is none and "10" is severe.

Patients were also asked to complete a validated short form Spielberger State Trait Anxiety Inventory (STAI-6) questionnaire<sup>11</sup> at baseline and after both EG Scan and C-EGD procedures. STAI-6 scores were calculated as per the developers' guidelines, with clinically significant anxiety considered to be a score of  $\geq 40$ <sup>11</sup>.

## Outcome measures

Study outcome measures included:

1. The technical feasibility and quality of the endoscopic examinations measured as: (i) rate of successful intubation (the ability to traverse the upper esophageal sphincter and visualize the esophageal mucosa); (ii) rate of complete visualization of the tubular esophagus, squamocolumnar junction, and gastroesophageal junction; and (iii) duration of EG Scan examination (time from intubation to extubation).
2. Safety of procedures measured as the rate of serious adverse events or need for hospitalization assessed immediately and within 14 days (telephone call from the study coordinator) after procedures.
3. Patients' acceptability of both procedures measured using validated questionnaires as detailed above.
4. The accuracy of EG Scan (index test) in detecting: (i) any length BE; (ii) long segment BE (LSBE) defined as circumferential (C) or maximal (M) length  $\geq 3$  cm by Prague criteria<sup>9</sup>; and (iii) short segment BE (SSBE) defined as C or M  $< 3$  cm using C-EGD as the reference standard.

## Statistical analysis

Data on the diagnostic accuracy and acceptability of this novel screening tool compared to C-EGD were not available to reliably inform sample size calculations. We assessed a group of 200 patients with the aim to include approximately 50% with known BE (prevalence). Based upon clinical experience, we expected the EG Scan sensitivity to be 0.85 to 0.90. In this scenario, a sample size of 141 to 200 patients will give us a margin of error of  $\pm 0.07$ , which will be clinically meaningful to evaluate this device as a diagnostic test for BE<sup>12</sup>. We used paired t-test (normally distributed differences) and Wilcoxon signed rank test (non-normally distributed differences) to compare measurements of continuous variables. The

Chi-squared or Fisher exact tests were used to compare categorical variables. Statistical computations were performed using the Stata version 12.0 software (Stata Corporation, College Station, Texas, USA).

## RESULTS

### Baseline characteristics

Two hundred patients were enrolled (Nottingham n=50; Cambridge n=50; Mayo Clinic n=100). The mean ( $\pm$  standard deviation (SD)) age was 58 years ( $\pm$ 14) and BE prevalence was 53%. The median (interquartile range (IQR)) length of BE was C0 (IQR 0-2) and M2 (IQR 1-4). Baseline characteristics of all participants are outlined in table 1.

### Technical feasibility, quality and safety

178 out of 200 patients (89%) completed both procedures and included in the analysis. Twenty two patients (11%) failed EG Scan due to the inability to intubate the nasopharynx. Those were equally split between the UK (n=11; 5.5%) and the USA (n=11; 5.5%) centers. (Figure 2). The rate of complete visualization was similar between the two techniques (Table 2). The mean duration of the EG Scan examination was 4.0 ( $\pm$  4.0) minutes. 120 out of 178 (67%) C-EGD procedures were performed under sedation. Of those, 110 received intravenous midazolam (median dose 5 mg; IQR 3-6) with or without intravenous pethidine (n=35; median dose 50 mg; IQR 0-62.5) or intravenous fentanyl (n=70; median dose 100 mcg; IQR 75-100). Ten patients received propofol sedation.

There were 5 cases of non-serious adverse events which included: (i) probe technical failure (n=2) towards the end of procedures where the up/down lever at the handle failed to achieve tip deflection and the procedure was terminated; (ii) two patients (1.1%) experienced vasovagal symptoms after abdominal distension secondary to air insufflation during the procedure. This self-terminated after a short period of observation; and (iii) one patient

(0.55%) developed self-limiting epistaxis. All those 5 patients were included in the analysis. No serious adverse events occurred.

### **Acceptability**

The overall tolerability (VAS scores) was better with EG Scan compared to C-EGD (Table 2). When stratified by sedation and center location, the VAS scores were comparable between the EG scan and C-EGD in the subgroup of patients that either received sedation or where from the USA center. There was a significant reduction in the mean ( $\pm$  standard error of the mean (SEM)) anxiety scores post EG Scan (30.5  $\pm$ 0.8;  $p=0.0003$ ) and post C-EGD (28.7  $\pm$ 0.9;  $p<0.0001$ ) compared to baseline (33.4  $\pm$ 0.8).

### **Accuracy**

Ninety four out of the 178 patients (53%) had BE (n=40 LSBE; n=54 SSBE). Data on accuracy are shown in table 3. The EG Scan missed 9 cases of BE, 2 of those were LSBE (Figure 2). In both of those, the squamo-columnar junction was poorly visualized with white light imaging on C-EGD and had to be confirmed with narrow band imaging. Example findings of EG Scan are shown in Figure 3.

## **DISCUSSION**

### **Principal findings**

Results from this multicenter study evaluating the clinical feasibility of using the EG Scan device as a clinic-based screening test for BE demonstrate that the procedure is safe, well tolerated, and accurate, when compared to C-EGD. Significantly more patients preferred the EG Scan over C-EGD independent of sedation use for the latter.

The difference in technical success rate for EG Scan compared to C-EGD in this study was -11% (89% vs. 100%, respectively). This is larger than expected compared to values reported in the literature<sup>4</sup>. All operators had a comparably limited experience of using the EG Scan at

baseline, therefore, a learning curve which may impact on both the technical and diagnostic performance of this technique might be present. We have previously demonstrated that studies using TNE <5.9 mm insertion diameter reported significantly higher success rates compared to those using  $\geq 5.9$  mm<sup>4</sup>. The insertion diameter of the EG Scan was 6.1 mm which is relatively large compared to other modern TNE devices<sup>5</sup>. A third generation EG Scan prototype with a smaller insertion diameter of 5.0 mm has been developed. This may allow for further improvements in device performance compared to the current prototype.

Results on accuracy of EG Scan for the detection of BE in this study were comparable to those reported for other conventional TNE devices (non-portable and non-disposable)<sup>13, 14</sup>. Shariff et al<sup>13</sup>, reported a sensitivity and specificity of 0.98 and 0.99, respectively, for TNE using a FUJINON endoscope (EG530N, FUJIFILM Europe GmbH, Düsseldorf, Germany) with a 5.9 mm insertion diameter. However, they only included patients with a minimum circumferential length BE of 2 cm and all procedures were performed in a dedicated endoscopy suite. Our data suggest that undertaking TNE in a clinic room using a significantly more compact device (EG Scan) can still achieve high sensitivity in this subgroup of patients with longer segment BE.

One limitation of the EG Scan compared to other TNE devices and C-EGD is the lack of a working channel, hence it is not possible to obtain biopsy samples from endoscopically suspected areas of BE. Nevertheless, it must be emphasized that we evaluated this device as a potential tool for future use in a two-step BE screening program in the primary care setting. If such a program is implemented using this technology, then the issue of biopsy acquisition becomes less critical, because all cases with suspected BE will require a clinical C-EGD for surveillance biopsies and risk stratification as per current practice. The cost of the EG Scan probe compared to other tools needs to be taken into account, however, this can vary significantly depending on supply and demand. Moreover, there are several other important issues to consider when comparing the EG Scan to other screening tools, such as turnover time, screening uptake, accuracy, acceptability, yield for other pathologies, and

impact on quality of life. These factors must be incorporated into a cost-effectiveness modelling study to evaluate different screening approaches.

A capsule sponge (Cytosponge™) coupled with a biomarker (TFF3) has been evaluated in a case-control and in a primary care setting. In the case-control study (1100 patients (647 cases and 463 controls)<sup>15</sup>, the success rate of the capsule sponge was 94% and the overall sensitivity and specificity for BE  $\geq$ C1 or  $\geq$ M3 were 0.80 (95%CI 0.76-0.83) and 0.92 (95%CI 0.90-0.95), respectively. In the primary care setting with a prevalence of 3%, the sensitivity and specificity of the test for the detection of BE  $\geq$ C1 were 0.73 and 0.94, respectively<sup>16</sup>. Screening using a non-endoscopic device was also found to be cost-effective in a separate economic modelling study<sup>17</sup>. The procedure can be performed by less skilled operators with potential for widespread applicability. The sampling has advantages for the evaluation of cellular and molecular features suggestive of inflammation, infection, intestinal metaplasia and dysplasia<sup>18, 19</sup>, however on the other hand it will not provide real time visualization of the BE segment as well as other high risk features associated with it, such as erosive esophagitis, ulcers, strictures, and polypoid lesions (Figure 3). All these trade-offs need to be carefully weighed when comparing different screening technologies.

Screening tests should be acceptable to patients with minimal psychological impact in order to improve the uptake and cost-effectiveness of the screening program<sup>20</sup>. Data from this study demonstrate a positive impact of EG Scan on patients' satisfaction with a significant reduction in anxiety scores after procedures. TNE screening for BE can be performed successfully by physician extenders after a short training program<sup>21</sup>. This may reduce operator costs and increase access to future screening programs. TNE screening was also found to be more cost effective than C-EGD screening with lower direct and indirect costs<sup>3</sup>.

<sup>22</sup>.

### **Study strengths and limitations**

This multi-center study had several strengths and limitations. The trial conduct and reporting conforms to current guidelines for undertaking diagnostic accuracy studies which is an important strength<sup>8, 23</sup>. We used validated VAS<sup>10</sup> and 3-item (EG Scan or C-EGD or either) questionnaires to measure tolerability and preference, respectively. Those were self-administered at home with the endoscopist blinded to eliminate interviewer bias<sup>24</sup>. The response rate was 94% (168 out of 178) for both VAS and preference questionnaires (Table 2), hence response bias remains unlikely. Moreover, patients were offered the choice of “either” for their procedure preference to minimize forced choice bias, where respondents who have no preference will be forced to select an answer (EG Scan or C-EGD) that may or may not reflect their true feelings<sup>24</sup>. We cannot rule out social desirability or obsequiousness bias where respondents may alter their questionnaire responses in the direction they perceive to be desired by the investigator<sup>24</sup>, however, this limitation pertains to the majority of questionnaire study designs. Patients were not offered monetary compensation nor any other incentive (such as an earlier appointment) to participate in the study.

This was a non-randomized cohort study and no pilot data were available to adequately inform sample size calculations. The order of procedures and operators should be randomized in future trials in order to eliminate bias in preference estimates towards one procedure or the other. Due to the performance of this study in tertiary centers using a case-control design, the prevalence of BE in this study was high compared to the general population<sup>6, 16</sup>. The diagnostic accuracy can be overestimated if the test is evaluated in patients already known to have the disease, rather than in a relevant screening population<sup>25</sup>. The proportion of false positive diagnoses will be higher and false negative ones will be lower when the current sensitivity and specificity is applied to lower prevalence populations (Supplementary box 1). However, for this initial study since the prevalence of BE is low<sup>26</sup>, we opted to enrich the study population with patients known to have BE in order to obtain estimates of sensitivity and specificity.

We did not evaluate interobserver agreement. The EG Scan was less sensitive in detecting SSBE compared to LSBE. This could be due to a limitation of the EG Scan imaging quality or could equally be a result of poor agreement between the EG Scan and C-EGD operators on the presence or absence of SSBE. Seven out of the 9 cases missed by the EG Scan had a circumferential length of 0 cm and maximal length of 1-2 cm (Figure 2). The interobserver agreement on presence of circumferential BE <1 cm is known to be poor (0.22) compared to BE  $\geq$ 1 cm (0.72)<sup>9</sup>.

### **Conclusions**

Clinic-based TNE using the EG Scan was feasible, safe, and highly acceptable by patients compared to C-EGD. The overall technical success rate of EG Scan was lower than expected compared to literature estimates for the TNE technique. This could be due to factors such as operator expertise and the insertion diameter of the EG Scan probe. EG Scan accuracy for the detection of BE was high. Future studies should evaluate the utility of this technique in the intended screening population. In particular, important outcomes such as participation rates, learning curve, yield of screening, and cost-effectiveness need to be assessed.

## TABLES

**Table 1:** Baseline characteristics of the study cohort (n=200). Data presented as number (%) or mean (+/- standard deviation) as applicable.

<b>Variable</b>	<b>No Barrett's (n=95)</b>	<b>Barrett's (n=105)</b>	<b>Total (n=200)</b>
<b>Age</b>	52.7 (+/-14.6)	62.5 (+/-11.7)	57.9 (+/-14.0)
<b>Male sex</b>	53 (55.8%)	81 (77.1%)	134 (67.0%)
<b>White ethnicity</b>	89 (93.7%)	104 (99.0%)	193 (96.5%)
<b>Body mass index</b>	28.4 (+/-5.6)	29.6 (+/-5.2)	29.0 (+/-5.4)
<b>Education</b>			
Primary	9 (9.6%)	20 (19.2%)	29 (14.7%)
Secondary	31 (33.0%)	39 (37.5%)	70 (35.4%)
College	26 (27.7%)	25 (24.0%)	51 (25.8%)
University	28 (29.8%)	20 (19.2%)	48 (24.2%)
<b>Smoking</b>	9 (9.5%)	10 (9.5%)	19 (9.5%)
<b>NSAIDs use</b>	18 (19.0%)	17 (16.2%)	35 (17.5%)
<b>Proton pump inhibitors use</b>	51 (53.7%)	99 (94.3%)	150 (75.0%)
<b>H2-receptors blockers use</b>	12 (12.6%)	12 (11.4%)	24 (12.0%)
<b>Aspirin use</b>	19 (20.0%)	31 (29.5%)	50 (25.0%)
<b>Family history EAC</b>	6 (6.3%)	10 (9.6%)	16 (8.0%)

NSAIDs, Non-steroidal anti-inflammatory drugs; EAC, esophageal adenocarcinoma.

**Table 2:** Technical feasibility, quality and acceptability of endoscopic assessments (n=200). Data presented as number (%), mean (+/- standard deviation), or median (interquartile range (IQR)).

Variable	EG Scan	C-EGD	P value
<b>Rate of successful intubation</b>	178 (89%)	200 (100%)	<0.001
<b>Rate of complete visualization†</b>	175 (98.3%)	177 (99.4%)	0.3146
<b>Discomfort scales</b> (0= none 10= worst)			
Gagging/retching	2 (IQR 0-3)	-	
Choking	0 (IQR 0-1)	-	
Discomfort	2 (IQR 1-3)	-	
Nasal pain (EG only)	1 (IQR 0-3)	-	
<b>VAS score total (n=168)‡</b>	7.2 (+/-2.0)	6.4 (+/-2.7)	0.0004
sedation subgroup (n=113)	7.1 (+/-2.0)	7.3 (+/-2.2)	0.4543
no sedation subgroup (n=55)	7.4 (+/-1.9)	4.4 (+/-2.0)	<0.001
UK centers subgroup (n=81)	7.3 (+/-2.0)	5.1 (+/-2.8)	<0.001
USA center subgroup (n=87)¶	7.2 (+/-2.0)	7.6 (+/-2.0)	0.1556
<b>Preference total (n=168)§</b>	91 (54.2%)	28 (16.7%)	<0.001
sedation subgroup (n=113)	50 (44.3%)	23 (20.4%)	<0.001

no sedation subgroup (n=55)	41 (74.5%)	5 (9.1%)	0.001
UK centers subgroup (n=81)	52 (64.2%)	13 (16.1%)	<0.001
USA center subgroup (n=87)¶	39 (44.8%)	15 (17.2%)	<0.001

C-EGD, conventional esophagogastroduodenoscopy; VAS, visual analogue scale; † calculated for patients who were successfully intubated and underwent both procedures (n=178). Visualization was incomplete in 3 patients (EG Scan) due to secretions and one patient (C-EGD) due to intolerance with constant gagging despite sedation; ‡ 168/178 returned the tolerability (VAS) and preference questionnaires; § 119/168 expressed preference for either EG Scan or C-EGD while the remaining 49/168 had no preference (either); ¶ all patients in this subgroup received sedation for C-EGD.

**Table 3:** Accuracy of the EG Scan for Barrett's esophagus (BE) diagnosis. Data presented as decimal fraction (95% confidence interval)

	Sensitivity	Specificity	AUROC
Any length BE	0.90 (0.83 – 0.96)	0.91 (0.82 – 0.96)	0.91 (0.86 – 0.95)
Long segment BE	0.95 (0.83 – 0.99)	1.0 (0.96 – 1.0)	0.98 (0.94 – 1.0)
Short segment BE	0.87 (0.75 – 0.95)	0.91 (0.82 – 0.96)	0.89 (0.83 – 0.94)

AUROC, area under the receiver operating characteristic curve

## FIGURE LEGENDS

**Figure 1:** The EG Scan™ II system. (A) the portable case with four main parts; (B) the image processor (top left), disposable probe (top right), air tube (bottom right) and hand-held controller (bottom left); (C) the system connected and ready for use; (D) close view of the

capsule probe tip. (*Reproduced with permission from Sami SS, et al. Copyright John Wiley and Sons*).

**Figure 2:** Study flowchart. BE, Barrett's esophagus; †8 cases false positive on EG Scan, 7 were classed as C0M1 and 1 classed as C0M2 by Prague classification; ‡EG Scan missed 9 cases of BE, those were classed as C5M6 (n=1), C9M9 (n=1), C0M2 (n=4), C0M1 (n=3) by Prague classification.

**Figure 3:** Image quality and example findings of EG Scan. (A) Normal; (B, C) Barrett's esophagus; (D) Schatzki's ring; (E) Erosive esophagitis; (F) Esophageal adenocarcinoma.

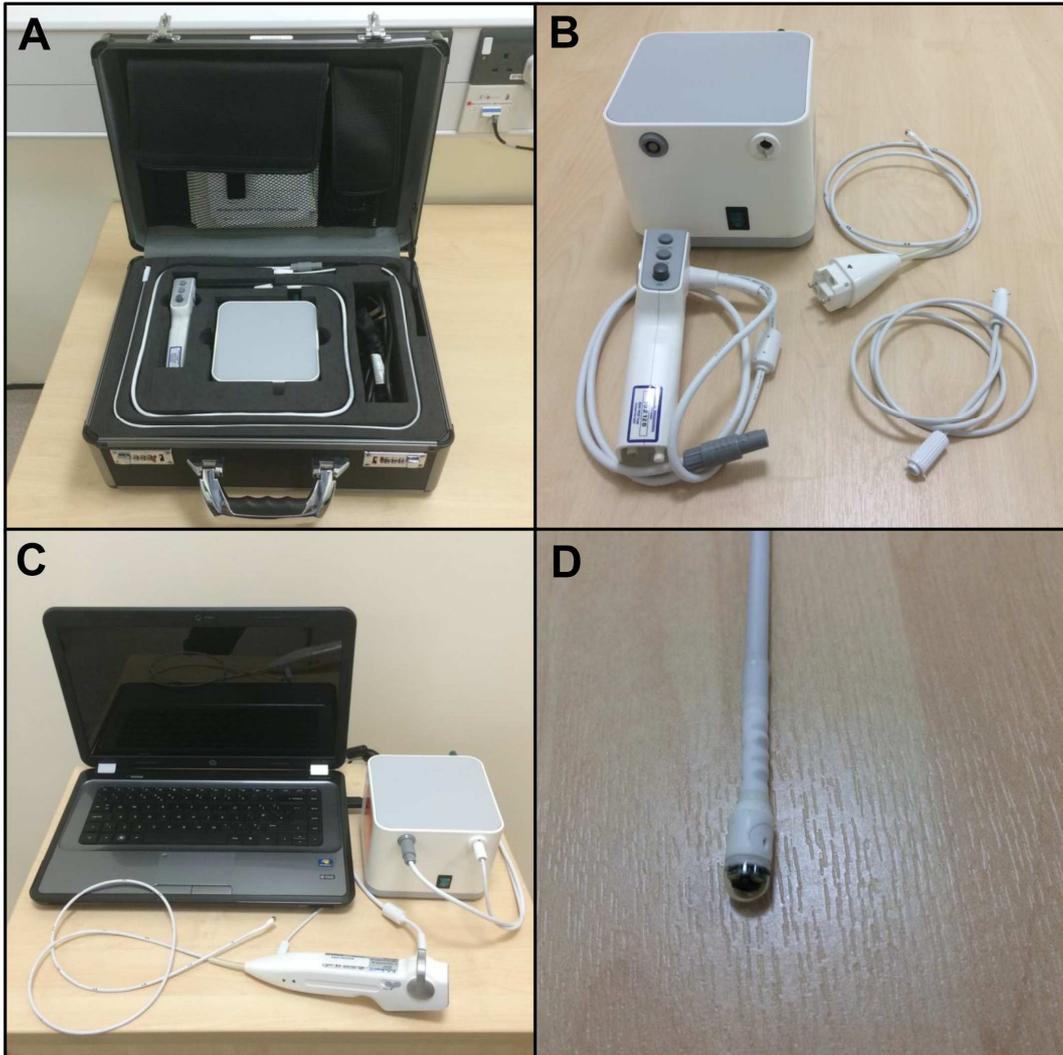
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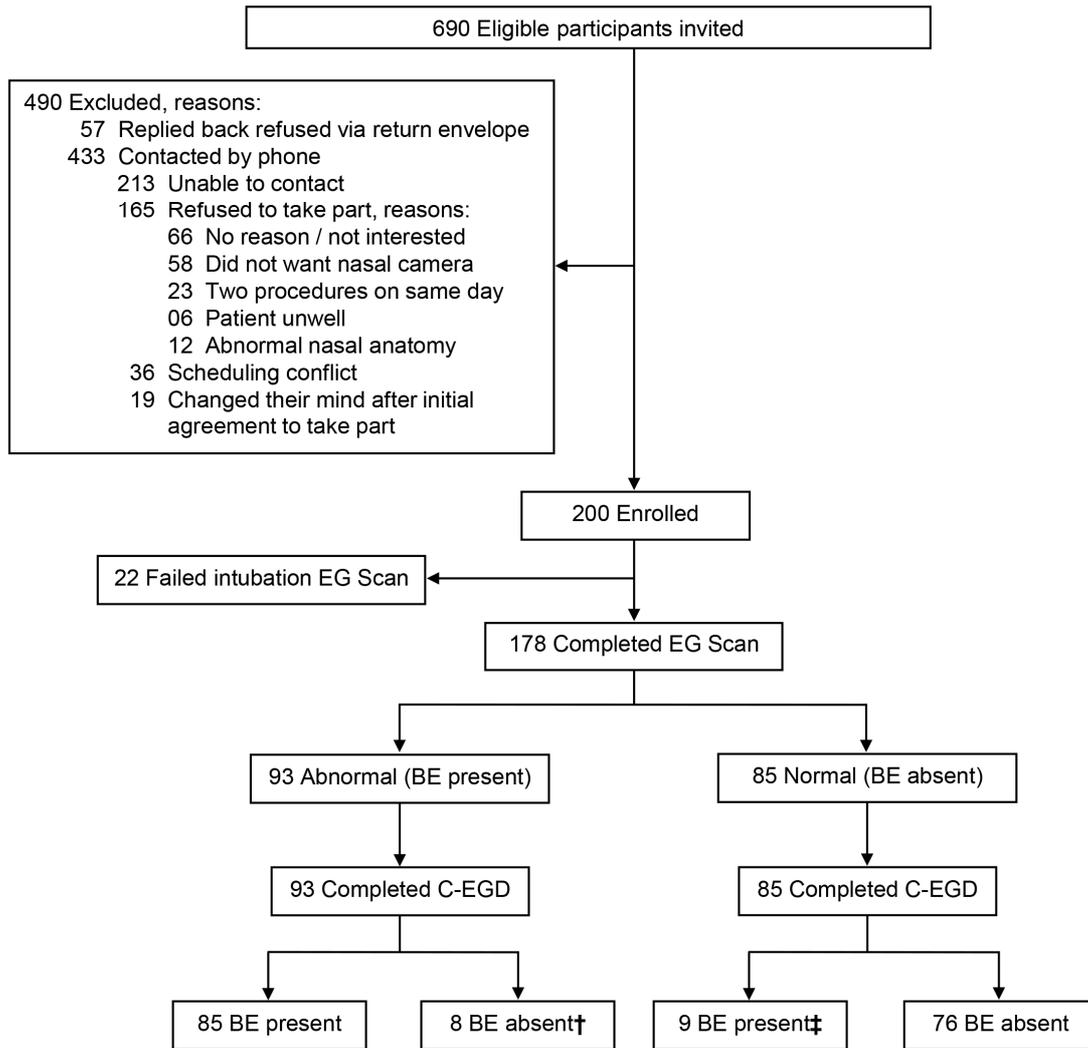
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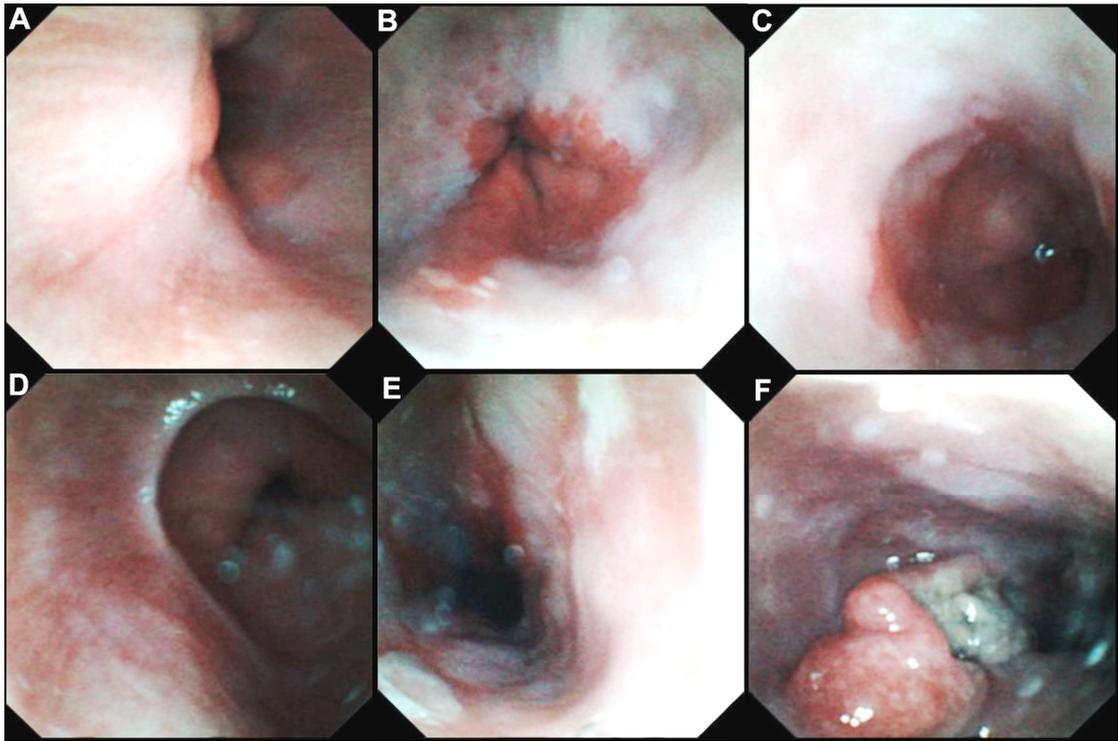
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## Significance of this study

### Background

- Screening for Barrett's esophagus (BE) with conventional esophagogastroduodenoscopy (C-EGD) is not cost effective.
- Unsedated transnasal endoscopy (TNE) is safe, accurate and acceptable alternative to C-EGD.
- Existing TNE devices have limited applicability for widespread use in the community setting due to limited portability and the need for decontamination.

### Findings

- Clinic-based TNE using the EG Scan device was safe, feasible and acceptable.
- A higher proportion of patients preferred the EG Scan over C-EGD regardless of the use of sedation for the latter.
- The EG Scan was accurate for the detection of BE of any length with superior accuracy for long segment compared to short segment BE.

### Implications for patient care

- This device could potentially serve as a tool for screening populations at risk for BE.
- Future studies should evaluate the utility of this technique in the intended screening population. In particular, important aspects such as participation rates, operator training, and yield of screening need to be explored.

**Supplementary table 1: The EG Scan™ II system components.**

1. A disposable probe (diameter 3.4 mm, length 1088 mm) which is made from human compliance plastic and sealed with a biocompatible adhesive. The probe is designed for single use; therefore the risk of cross infection is eliminated. It contains:
  - a) Capsule at the tip (diameter 6.1 mm) which produces images at a speed of 30 frames per second with a 125° field of view and 3-50 mm view depth. The camera capsule comprises four white light-emitting diodes (LEDs) and a complementary metal-oxide semiconductor (CMOS) image sensor with 400×400 pixel array.
  - b) Bending wire to facilitate tip deflection with bending angle of 160° up/160° down.
  - c) Data connector to transmit captured images from tip of the capsule to the processor.
  - d) Air insufflation channel. There is no suction or biopsy capability.
2. A hand-held controller which has freeze, capture and air insufflation buttons with an up/down lever at the handle to facilitate tip deflection. The probe is attached to the controller.
3. An image processor which incorporates a free air displacement system (5L/min). Images are transmitted from the tip of the probe to the processor and then displayed on a laptop computer screen via USB connection. The E.G. view™ computer software is used to visualize videos and images.
4. An air tube which connects the processor to the probe in order to facilitate air insufflation during the procedure.

**Supplementary box 1: Impact of disease prevalence on positive and negative predictive values of the test (based on current sensitivity and specificity).**

**A- Example calculation:** at a study prevalence of 0.53 for Barrett's esophagus (BE) = 0.53 with "disease" and 0.47 with "no disease", therefore proportion of patients with true positive (TP) result = sensitivity (0.90) \* prevalence (0.53) = 0.48 and the remaining 0.05 are false negative (FN). Similarly, proportion of true negative (TN) = specificity (0.91) \* 1-prevalence (0.47) = 0.43 and the remaining 0.04 are false positive (FP).

Therefore: positive predictive value (PPV) =  $TP/TP+FP = 0.48/0.48+0.04 = 0.92$

Negative predictive value (NPV) =  $TN/TN+FN = 0.43/0.43+0.05 = 0.90$

**B- Example calculation:** at a lower prevalence of 0.08 for BE = 0.08 with "disease" and 0.92 with "no disease", therefore proportion of patients with TP result = sensitivity (0.90) \* prevalence (0.08) = 0.072 and the remaining 0.008 are FN. Similarly, proportion of TN = specificity (0.91) \* 1-prevalence (0.92) = 0.84 and the remaining 0.08 are FP.

Therefore: positive predictive value (PPV) =  $TP/TP+FP = 0.072/0.072+0.08 = 0.47$

Negative predictive value (NPV) =  $TN/TN+FN = 0.84/0.84+0.008 = 0.99$