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Mass Screening for Barrett's esophagus: Myth or Reality?

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Esophageal adenocarcinoma (EAC) is the main histologic type of esophageal cancer in the West with an estimated incidence of 52,000 cases worldwide in 2012.[1] Mathematical models predict a continued increase in EAC incidence with a near doubling of mortality in the United States between 2011 and 2030 compared to the previous 20 years.[2] Over 40 % of patients with EAC are diagnosed after the disease has metastasized, which translates to dismal survival.[3] Hope lies in the fact that the cancer can be reliably cured when detected early and if detected at a mucosal stage, it can even be treated endoscopically .[4] Moreover, advances in endoscopic eradication therapy for dysplastic Barrett's esophagus (BE) now make it possible to prevent the development of this cancer.[5,6] Early detection of EAC and/or its prevention by endoscopic eradication therapy will have significant impact in reducing the mortality from this lethal disease only if effective mass screening and surveillance programs can be developed.

Most, if not all EAC is thought to arise from BE. Recent evidence suggests that surveillance following a diagnosis of BE is associated with detection of earlier stage EAC and a modest survival benefit.[7] Up to 5.6% of the adult US population are estimated to have BE but very few are diagnosed.[8] The reasons are many: the current standard screening technique, sedated endoscopy, is invasive and expensive and therefore recommended only for selected gastroesophageal reflux disease (GERD) patients with multiple risk factors for BE.[9,10] The limitations are evident, as a GERD based strategy will fail in the 40% of EAC patients who do not have any prior reflux symptoms.[11] Moreover, patients and primary care physicians are reluctant to undergo endoscopy, especially when GERD symptoms are well controlled. Hence, the diagnosis of BE is made prior to cancer diagnosis in less than 10% of EAC cases. [12] Therefore, a need exists for a safe, effective, acceptable, nonendoscopic screening method, which can be applied for large scale mass screening of BE.

Numerous alternatives to sedated endoscopy for BE screening are intensely being investigated (figure 1). This issue of *Clinical Gastroenterology and Hepatology* reports on

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two such techniques, a new disposable transnasal video capsule, EG scan[13] and a swallowable, cytological sampling sponge device, Cytosponge.[14] The EG Scan is a thin video capsule inserted trans-nasally for endoscopic imaging of the distal esophagus with the advantage of a disposable video-chip and portable image processing. In a tertiary care population with a high prevalence of BE, this technology showed 90% sensitivity and 91% specificity in the 89% of subjects that could be examined. If the cost of EG scan is reduced, nasal intubation rate improved, and primary care practitioners are trained to recognize BE, this technology could enable convenient office based screening of BE. The other device is Cytosponge, which samples the esophagus with an encapsulated sponge and relies on an immunohistochemical marker, trefoil factor 3 for the cytological diagnosis of BE. This device and marker combination has been studied more extensively in case control studies as well as prospective screening studies with a sensitivity of 73–80% and specificity of 92–94% for diagnosing BE.[15, 16] This technology has been commercialized and is being evaluated in a large screening trial in the United Kingdom. In the United States, although the technology is FDA approved, it is currently being re-designed to prevent the sponge detaching from the string during withdrawal. The current study is a pooled analysis of previous Cytosponge studies of over 2500 subjects that shows that the device is extremely safe. There was only one device detachment and one limited bleeding episode related to the abrasiveness of the sponge. The inability to swallow the device in this pooled analysis was less than 5%. Both these studies advance the efforts to develop alternative strategies to sedated endoscopy that could enable more widespread BE screening.

Much can be learned from attempts to develop unsedated trans-nasal esophagoscopy (TNE) as an alternative to sedated endoscopy for BE screening.[17,18]Although TNE is less expensive, nearly as sensitive and specific as sedated endoscopy, and the majority of subjects who undergo the procedure prefer TNE to sedated endoscopy, the procedure has had limited acceptance in the United States[19] perhaps due to misperception that it will be uncomfortable. Thus the EG scan technology will not only have to be available at an acceptable cost but will also need to overcome the attitudinal barriers that have limited the utilization of TNE.

Other methods for BE screening that are being developed include a tethered optical coherence tomographic imaging capsule (with sensitivity and specificity for diagnosis of BE of 77 and 86% respectively),[20] an electronic nose that detects volatile organic compounds using mass spectrophotometry (82% sensitivity, 80% specificity for BE detection),[21] liquid biopsies to detect circulating microRNAs, and an encapsulated balloon distal esophageal sampling device that assays methylated DNA markers.[22] The JASSS (Joe, Amitabh, Sandy Swallowable Sampling) device is a capsule with a retracted balloon, which is tethered to a soft silicone catheter. Once the capsule reaches the stomach after swallowing, the balloon with surface features is inflated and withdrawn to sample the lower esophageal sphincter and distal esophagus. The balloon with the distal esophageal sample is then vacuum inverted back into the capsule to protect it from contamination during withdrawal, and the material adherent to the balloon is assayed for methylated VIM and CCNA1. Methylated DNA biomarkers are attractive because these assays are automatable, inexpensive, and already FDA approved for other diagnostics. This Esocheck technology using the JASSS device, which has recently been licensed for commercialization has a 90% sensitivity and a 92% specificity for diagnosing BE.[22] A different set of methylated DNA markers (VAV3 and

ZNF682) has also been reported recently to be equally accurate in combination with a sponge on a string as a BE diagnostic test.[23] Studies will be required to compare the selective distal esophageal sampling approach of the JASSS device to the whole esophageal sampling approach of the Cytosponge and other sponge devices.

In conclusion, any non-endoscopic screening technique will need to meet the following criteria to become part of standard clinical practice: 1. Specificity >90% and high sensitivity, preferably 90% or higher; 2. Low cost - preferably less than a quarter that of sedated endoscopy; 3. High uptake in at risk population – this implies not just the research subjects but majority of subjects who are at risk for BE are willing to have the test; and 4. Easily implemented – portable to primary clinic setting or performed as part of routine gastroenterology practice. Trials to assess the efficacy and acceptance rates of the various non-endoscopic screening techniques continue to evolve making it possible to start considering mass screening. Ultimately, the utility of any screening test will depend on its ability to reduce the morbidity and mortality from esophageal cancer. And until then, the search continues….

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Abbreviations:

BE	Barrett’s esophagus
EAC	Esophageal adenocarcinoma
GERD	gastroesophageal reflux disease
TNE	trans-nasal esophagoscopy

REFERENCES:

1. Arnold M, Soerjomataram I, Ferlay J, et al.: Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015; 64: 381–387. [PubMed: 25320104]
2. Kong CY, Kroep S, Curtius K, et al.: Exploring the recent trend in esophageal adenocarcinoma incidence and mortality using comparative simulation modeling. Cancer Epidemiol Biomarkers Prev. 2014; 23:997–1006. [PubMed: 24692500]
3. Hur C, Miller M, Kong CY, et al. Trends in esophageal adenocarcinoma incidence and mortality. Cancer. 2013; 119:1149–1158. [PubMed: 23303625]
4. Pech O, May A, Manner H, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology. 2014;146(3):652–660. [PubMed: 24269290]
5. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett’s esophagus with dysplasia. N Engl J Med. 2009;360(22):2277–88. [PubMed: 19474425]
6. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA. 2014;311(12):1209–17. [PubMed: 24668102]

7. Codipilly DC, Chandar AK, Singh S, et al. The Effect of Endoscopic Surveillance in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis. Gastroenterology. 2018; 154(8): 2068–86. [PubMed: 29458154]
8. Hayeck TJ, Kong CY, Spechler SJ, et al. The prevalence of Barrett's esophagus in the US: estimates from a simulation model confirmed by SEER data. Dis Esophagus. 2010; 23(6):451–7. [PubMed: 20353441]
9. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011;140(3):1084–91. [PubMed: 21376940]
10. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016;111(1):30–50. [PubMed: 26526079]
11. Chak A, Faulx A, Eng C, et al. Gastroesophageal reflux symptoms in patients with adenocarcinoma of the esophagus or cardia. Cancer. 2006;107(9):2160–6. [PubMed: 17019737]
12. Dulai GS, Guha S, Kahn KL, et al. Preoperative prevalence of Barrett's esophagus in esophageal adenocarcinoma: a systematic review. Gastroenterology. 2002;122(1):26–33. [PubMed: 11781277]
13. Sami SS, Iyer PG, Pophali P, et al. Acceptability, Accuracy and Safety of Disposable Transnasal Capsule Endoscopy for Barrett's Esophagus Screening. Clin Gastroenterol Hepatol. 2018 8 2 pii: S1542–3565(18)30743–2.doi: 10.1016/j.cgh.2018.07.019. [Epub ahead of print]
14. Januszewicz W, Tan WK, Lehovsky K, et al. Safety and acceptability of a non-endoscopic esophageal sampling device - Cytosponge(®): a systematic review of multi-center data. Clin Gastroenterol Hepatol. 2018 8 9 pii:S1542–3565(18)30809–7. doi: 10.1016/j.cgh.2018.07.043. [Epub ahead of print]
15. Kadri SR, Lao-Sirieix P, O'Donovan M, et al. Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. BMJ.341:c4372.
16. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, et al. 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 Med. 2015;12(1):e1001780. [PubMed: 25634542]
17. Atkinson M, Das A, Faulx A, et al. Ultrathin esophagoscopy in screening for Barrett's esophagus at a Veterans Administration Hospital: easy access does not lead to referrals. Am J Gastroenterol. 2008;103(1):92–7. [PubMed: 17764497]
18. Sorbi D, Chak A. Unsedated EGD. Gastrointest Endosc. 2003;58(1):102–10. [PubMed: 12838235]
19. Faulx AL, Vela S, Das A, et al. The changing landscape of practice patterns regarding unsedated endoscopy and propofol use: a national Web survey. Gastrointest Endosc. 2005;62(1):9–15. [PubMed: 15990813]
20. Bhardwaj A, Hollenbeak CS, Pooran N, et al. A Meta-Analysis of the Diagnostic Accuracy of Esophageal Capsule Endoscopy for Barrett's Esophagus in Patients With Gastroesophageal Reflux Disease. Am J Gastroenterol 2009; 104: 1533–1539. [PubMed: 19491867]
21. Chan DK, Zakko L, Visrodia KH, et al. Breath Testing for Barrett's Esophagus Using Exhaled Volatile Organic Compound Profiling With an Electronic Nose Device. Gastroenterology 2017; 152: 24–26. [PubMed: 27825962]
22. Moinova HR, LaFramboise T, Lutterbaugh JD, et al. Identifying DNA methylation biomarkers for non-endoscopic detection of Barrett's esophagus. Sci Transl Med. 2018;10(424).
23. Iyer PG, Taylor WR, Johnson ML, et al. Highly Discriminant Methylated DNA Markers for the Non-endoscopic Detection of Barrett's Esophagus. Am J Gastroenterol. 2018 6 12. doi: 10.1038/s41395-018-0107-7. [Epub ahead of print]

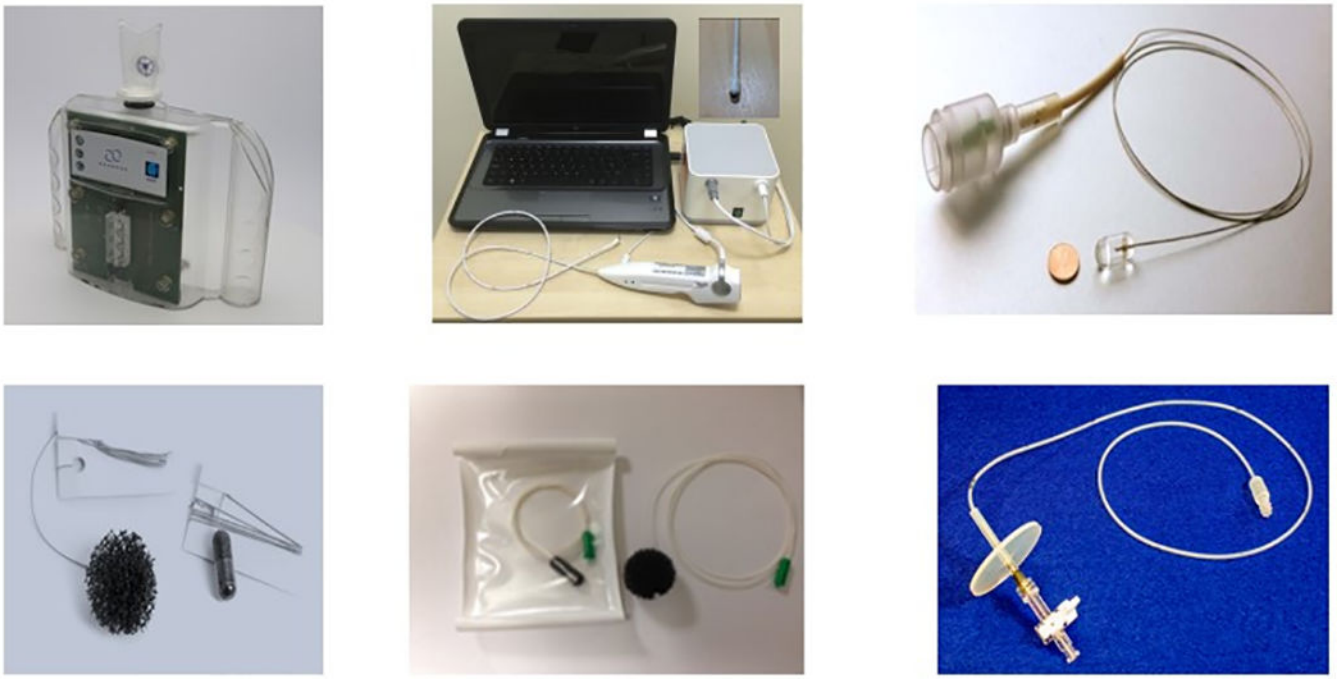

Figure 1:

Top Panel: Left corner: Electronic nose (courtesy of The eNose company, Netherlands); Middle: EG scan with tip in the inset (courtesy Dr. PG Iyer); Right corner: Tethered Capsule (with permission from Elsevier); **Bottom Panel**: Left corner: Cytosponge (courtesy of Dr. Rebecca Fitzgerald); Middle: Sponge on string (SOS) device(courtesy of Dr. PG Iyer) ; Right corner: JASSS balloon (contributed by Dr. Amitabh Chak).