Enhancing the Diagnostic Yield of EGD for Diagnosis of Barrett Esophagus Through Methylated DNA Biomarker Triage

Jayde E. Kurland, MD,[1] Sheena B. Patel, MD,[1] Richard Englehardt, MD,[2] Seper Dezfoli, MD,[3] Daniel M. Tseng, MD,[4] Michael W. Foutz, MD,[5] Paul S. Bradley, MD,[6] Badi Eghterafi, DO,[7] Victoria T. Lee, MD,[8] Suman Verma, MD, PhD,[8] Brian J. deGuzman, MD,[8] and Lishan Aklog, MD[8]

[1]Gastro Health, Lima, Ohio

[2]Bariatric Medical Institute of Texas, San Antonio, Texas

[3]Cedars-Sinai Medical Center, Los Angeles, California

[4]Northwest Minimally Invasive Surgery, Portland, Oregon

[5]Advanced Family Medicine, Kuna, Idaho

[6]Savii Health, Savannah, Georgia

[7]Valley Hospital Medical Center, Las Vegas, Nevada

[8]Lucid Diagnostics, New York, New York

Corresponding author:
Victoria T. Lee, MD
360 Madison Avenue, Floor 15
New York, NY 10017
Tel: (425) 218-6535
E-mail: VTL@pavmed.com

Abstract: Background: EsoGuard (EG) is a methylated DNA assay for cells collected nonendoscopically with EsoCheck for detection of Barrett esophagus (BE) and can be utilized as a triage to esophagogastroduodenoscopy (EGD) in patients meeting clinical criteria for BE screening. EG triage may enrich the population undergoing EGD, increasing BE diagnosis without overburdening endoscopy resources. Aim: To test the hypothesis that EGDs performed on patients who test positive on EG have higher diagnostic yields than screening EGDs alone. Methods: We collected real-world retrospective data from EG-positive patients for whom EGD diagnoses were available. The diagnostic yield of these EGDs was measured by the BE detection rate. The yield of screening EGDs was estimated by literature-established disease prevalence (10.6%). The hypothesis was tested using t-test for single proportions at a one-sided 5% significance level. Results: Among 209 patients, 60 (28.7%) had specialized intestinal metaplasia but 10 (4.8%) had less than 1 cm of nondysplastic disease. Because the American College of Gastroenterology (ACG) definition of BE requires disease length of at least 1 cm, these patients were excluded from analysis. In the analyzed population, we observed a 2.4-fold increase in BE detection compared with the 10.6% performance goal. There was a 2.7-fold increase in the cohort meeting ACG screening criteria and a 2.5-fold increase among those meeting ACG criteria who were aged 65 years and older. Conclusion: EG triage enriches the population undergoing EGD for BE detection. Compared with screening EGD alone, it improves diagnostic yield. This may help direct more efficient use of endoscopy resources to improve disease detection in at-risk patients.

Keywords
Barrett esophagus, EsoGuard, EsoCheck, non-endoscopic screening, methylated DNA biomarker, esophagogastroduodenoscopy

Barrett esophagus (BE) is the only known precursor for esophageal adenocarcinoma (EAC), the most common type of esophageal cancer in the United States.[1] Among patients with BE, the risk of developing EAC is 30 to 152 times higher than in the general population.[2] In contrast to the lethality of EAC and its approximately 80% 5-year mortality rate,[3] endoscopic eradication therapies can achieve complete eradication of BE in up to 80% to 90% of cases, underlying the importance of BE screening.[4-7] The American College of Gastroenterology (ACG) recommends BE screening for patients with chronic gastroesophageal reflux disease (GERD) and 3 or more of the following risk factors: male sex, White race, age greater than 50 years, obesity, history of tobacco smoking, and history of BE/EAC in a first-degree relative.[8] However, at-risk patients can also be asymptomatic or have atypical reflux symptoms.[9,10] Additionally, use of acid suppressive medications is common and although they reduce or even completely control GERD symptoms, the risk of BE is not eliminated.[11,12] These patients are less likely to seek endoscopic evaluation, leading to missed BE diagnoses and missed opportunities to intervene before malignant progression. As such, the American Gastroenterological Association (AGA) published recommendations in 2022 for screening patients with any 3 or more BE/EAC risk factors, without specifying GERD as a mandatory prerequisite.[13] However, only approximately 10% of eligible patients ever undergo esophagogastroduodenoscopy (EGD) for BE evaluation, attributed to a multitude of reasons, including lack of referrals by primary care providers (PCPs) and PCP unfamiliarity with gastroenterology guidelines.[14]

Both the ACG and AGA now include nonendoscopic cell collection combined with DNA biomarker(s) as an acceptable alternative to EGD for BE screening.[8,13] Noninvasive, in-office cell collection may increase access to BE screening for at-risk patients while streamlining endoscopy resource utilization. In this workflow, the nonendoscopic cell collection combined with a DNA biomarker test serves as a triage, and only patients with positive results are referred for EGD.[15,16] EsoGuard (EG; Lucid Diagnostics) is a commercially available methylated DNA biomarker assay that analyzes esophageal cells collected with the swallowable EsoCheck (Lucid Diagnostics) device. A prospective screening study of 124 patients at the Cleveland Veterans Affairs (VA) Medical Center demonstrated EG sensitivity and negative predictive value (NPV) of 92.9% and 98.6%, respectively.[17] Similar EG performance was previously published from two National Cancer Institute–funded case-control studies.[18,19] The Cleveland VA study also suggested that the use of EG for disease triage could increase the diagnostic yield of EGD 2.5-fold. To evaluate this in a real-world screening population, we retrospectively collected data from a larger sample of patients to test the hypothesis that the BE detection rate and, therefore, the diagnostic yield of EGDs is significantly increased in patients who first triage positive with EG.

Methods

Study Design and Data Collection

The protocol for this retrospective study was submitted to the Institutional Review Board and met requirements for a waiver of consent under 21 CFR 50.22. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. We collected data from patients who tested positive with EG in the 2023 calendar year and for whom follow-up EGD results were obtainable. Demographics and risk factors were collected from the test requisition forms stored in the EG commercial laboratory database. For statistical analysis purposes, any missing response(s) on risk factor questions were treated as absent/negative. Patients aged 65 years and older were categorized as Medicare-aged.

EsoGuard and EsoCheck

EG is a targeted next-generation sequencing DNA assay combined with a proprietary algorithm that examines the presence of methylation on the vimentin (*VIM*) and cyclin-A1 (*CCNA1*) genes for the qualitative detection of BE and EAC. Results are binary (ie, either positive or negative) based on a prespecified methylation cutoff. EG has been analytically validated as a laboratory-developed test performed in a Clinical Laboratory Improvement Amendments–certified, College of American Pathologists–accredited, and New York State–licensed laboratory (LucidDx Labs). Clinical performance of EG for detection of BE and EAC has been published elsewhere, demonstrating high sensitivity, specificity, and NPV.[17-19]

EG is performed on samples collected nonendoscopically with EsoCheck, a US Food and Drug Administration 510(k)-cleared, swallowable capsule-balloon device designed for circumferential, targeted collection of surface esophageal cells and their protected retrieval (Figure 1). Cell collection can be performed in any office setting without sedation and takes less than 3 minutes.[15,19]

Classification of Barrett Esophagus

The ACG defines BE as at least 1 cm of columnar epithelium on EGD with histopathologic findings of specialized intestinal metaplasia (SIM).[8] Patients with less than 1 cm of SIM in the distal esophagus (otherwise known as SIM of the esophagogastric junction; SIM-EGJ) are not considered positive for BE but can appropriately trigger a positive EG result because biomarker assays cannot distinguish disease length. Additionally, although patients

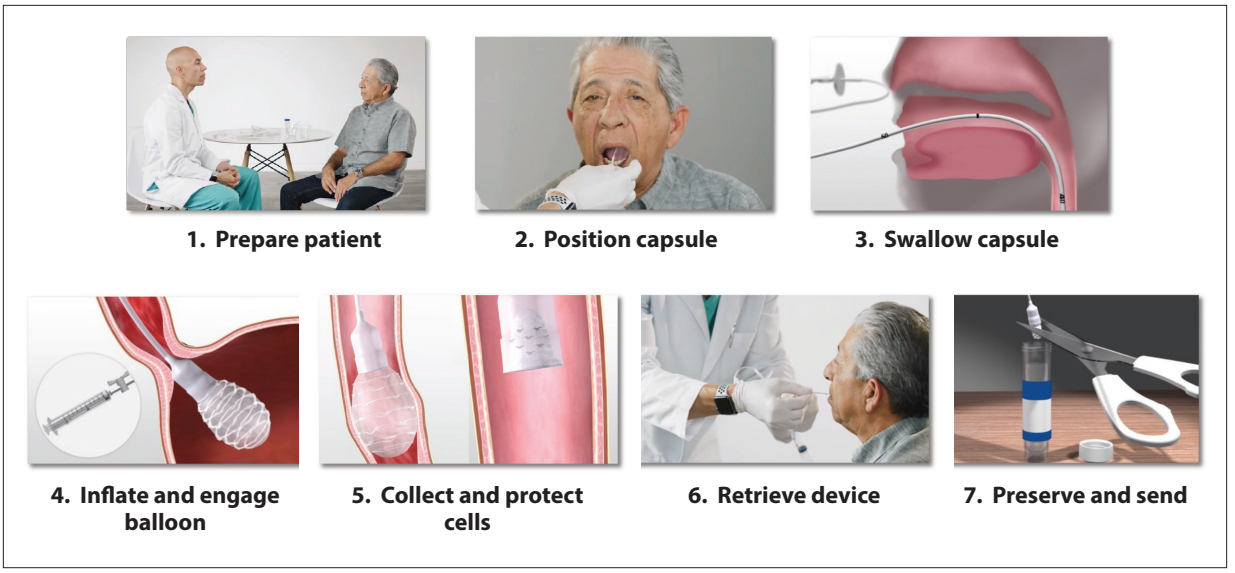

Figure 1. EsoCheck cell collection process. Image courtesy of Lucid Diagnostics; consent obtained from pictured individuals.

with SIM-EGJ have lower risk, they can still progress to EAC.[20] Thus, for study purposes, patients with SIM-EGJ were considered indefinite for BE rather than negative and were excluded from the primary outcome analysis. Patients with histopathologic findings of dysplasia were classified as positive for BE, irrespective of disease length.

Statistical Analysis

Summary statistics were performed for demographics and other baseline characteristics. The mean with standard deviation and median with interquartile range are presented where applicable. The chi-squared test was used for comparing categorical variables and the Kruskal-Wallis test for comparing group means. The BE detection rate represents the diagnostic yield of EGDs performed after a positive EG result, whereas the yield of screening EGD is assumed to equal the BE prevalence within an at-risk population. Literature demonstrates a BE prevalence of 10.6% in the US GERD population, serving as the performance goal for our primary outcome.[21] We hypothesized that triaging patients with EG prior to EGD would significantly increase the detection rate beyond this performance goal. The study hypothesis was tested using t-test for single proportions at a one-sided 5% significance level. The outcomes are presented using point estimates for frequency and percentages and normal two-sided 90% CI.

Results

We obtained EGD results from 209 patients who tested positive on EG in 2023, among several thousand commercial patients overall. Results came from 51 ordering providers, 74.5% (n=38) of whom were PCPs. Geographically, 44.0% (92/209) of patients were from the eastern United States (east of Mississippi), 35.9% (75/209) from the western United States (west of Colorado), and 20.1% (42/209) from the central United States.

Baseline patient characteristics are summarized in Table 1 according to EGD diagnosis. The average age was 64.1 years, and Medicare-aged patients accounted for 54.1% (113/209). The most common BE/EAC risk factors were age greater than 50 years (88.0%), White race (83.3%), and chronic GERD (78.5%). There was an increased prevalence of tobacco smoking among BE-positive (72.3%) and SIM-EGJ patients (77.8%), compared with BE-negative patients (49.3%). Although more BE patients met the ACG guideline criteria for screening than those without disease (66.0% vs 54.4%, respectively), this was not statistically significant.

The EGD diagnoses of patients meeting ACG criteria for BE screening were compared with those of patients meeting only AGA criteria (Table 2); results from the full study population are provided for reference. Overall, BE was detected in 23.9% (50/209), and 4.8% (10/209) had SIM-EGJ. Patients in the ACG screening cohort had a higher rate of BE (28.2% vs 18.5%, respectively) and a lower rate of SIM-EGJ (2.6% vs 7.6%, respectively), compared with the cohort meeting only AGA criteria. However, this was not statistically significant. The distribution of disease stage did not differ significantly between cohorts. Most disease was nondysplastic BE.

Figure 2 provides a breakdown of the different risk cohorts and their respective sample sizes contributing to the primary outcome analysis.

For our population of patients who tested positive with EG before undergoing EGD, the BE detection rates

Table 1. Demographics and Baseline Characteristics by EGD Diagnosis

	Indeterminate (SIM-EGJ) (N=10)	Negative for BE (N=149)	Positive for BE (N=50)	*P* value
Age, years				.0526[a]
Mean (SD)	61.9 (14.86)	65.3 (11.50)	61.1 (11.91)	
Median (IQR)	61.5 (53.5, 69.8)	66.9 (57.5, 74.2)	63.1 (50.5, 68.5)	
Age >50 years, n (%)				.0054[b]
No	2 (20.0%)	11 (7.4%)	12 (24.0%)	
Yes	8 (80.0%)	138 (92.6%)	38 (76.0%)	
Sex, n (%)				.0782[b]
Female	5 (50.0%)	68 (45.6%)	14 (28.0%)	
Male	5 (50.0%)	81 (54.4%)	36 (72.0%)	
Chronic GERD, n (%)				.0405[b]
No	5 (50.0%)	27 (18.1%)	13 (26.0%)	
Yes	5 (50.0%)	122 (81.9%)	37 (74.0%)	
White race, n (%)				.1786[b]
No	1 (11.1%)	27 (19.9%)	4 (8.5%)	
Yes	8 (88.9%)	109 (80.1%)	43 (91.5%)	
Missing	1	13	3	
Obese, n (%)				.2909[b]
No	3 (33.3%)	74 (53.6%)	21 (43.8%)	
Yes	6 (66.7%)	64 (46.4%)	27 (56.2%)	
Missing	1	11	2	
Tobacco smoking, n (%)				.0091[b]
No	2 (22.2%)	71 (50.7%)	13 (27.7%)	
Yes	7 (77.8%)	69 (49.3%)	34 (72.3%)	
Missing	1	9	3	
History of BE or EAC in a first-degree relative, n (%)				.5495[b]
No	8 (88.9%)	125 (92.6%)	42 (87.5%)	
Yes	1 (11.1%)	10 (7.4%)	6 (12.5%)	
Missing	1	14	2	
Total number of risk factors (age >50 years, male, GERD, White race, obese, tobacco smoking, family history)				.0182[a]
Mean (SD)	4.0 (1.15)	4.0 (0.92)	4.4 (0.97)	
Median (IQR)	4.0 (3.0, 4.0)	4.0 (3.0, 5.0)	4.0 (4.0, 5.0)	
Meet ACG screening criteria,[c] n (%)				.0848[b]
No	7 (70.0%)	68 (45.6%)	17 (34.0%)	
Yes	3 (30.0%)	81 (54.4%)	33 (66.0%)	
Meet AGA screening criteria,[c] n (%)				N/A
No	0 (0%)	0 (0%)	0 (0%)	
Yes	10 (100.0%)	149 (100.0%)	50 (100.0%)	
Medicare-aged cohort (age ≥65 years), n (%)				.2338[b]
No	6 (60.0%)	63 (42.3%)	27 (54.0%)	
Yes	4 (40.0%)	86 (57.7%)	23 (46.0%)	
Cohort meeting ACG screening criteria[c] and Medicare-aged, n (%)				.1314[b]
No	10 (100.0%)	106 (71.1%)	35 (70.0%)	
Yes	0 (0%)	43 (28.9%)	15 (30.0%)	

[a]Kruskal-Wallis *P* value. [b]Chi-square *P* value. *P* values are from comparing all 3 groups (SIM-EGJ, negative for BE, and positive for BE). [c]Missing values for a given risk factor are treated as absence of the risk factor.

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; BE, Barrett esophagus; EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; IQR, interquartile range; N/A, not applicable; SD, standard deviation; SIM-EGJ, specialized intestinal metaplasia of the esophagogastric junction.

Table 2. EGD Results in EsoGuard-Positive Patients: Patients Meeting ACG vs AGA Screening Criteria

	Overall (N=209) [90% CI]	Patients meeting ACG criteria for BE screening (n=117) [90% CI]	Patients meeting only AGA criteria for BE screening[a] (n=92) [90% CI]	*P* value
Diagnosis category				.085[b]
Indeterminate (SIM-EGJ)	4.8% (10/209) [2.6%, 8.0%]	2.6% (3/117) [0.7%, 6.5%]	7.6% (7/92) [3.6%, 13.8%]	
Negative	71.3% (149/209) [65.7%, 76.4%]	69.2% (81/117) [61.5%, 76.2%]	73.9% (68/92) [65.3%, 81.3%]	
Positive	23.9% (50/209) [19.1%, 29.3%]	28.2% (33/117) [21.4%, 35.8%]	18.5% (17/92) [12.1%, 26.4%]	
Disease stage				.609[b]
Nondysplastic BE	84.0% (42/50) [73.0%, 91.8%]	81.8% (27/33) [67.2%, 91.8%]	88.2% (15/17) [67.4%, 97.9%]	
Indefinite for dysplasia	6.0% (3/50) [1.7%, 14.8%]	9.1% (3/33) [2.5%, 21.9%]	0.0% (0/17) [0.0%, 16.2%]	
BE with low-grade dysplasia	4.0% (2/50) [0.7%, 12.1%]	3.0% (1/33) [0.2%, 13.6%]	5.9% (1/17) [0.3%, 25.0%]	
BE with high-grade dysplasia	6.0% (3/50) [1.7%, 14.8%]	6.1% (2/33) [1.1%, 17.9%]	5.9% (1/17) [0.3%, 25.0%]	

[a]By definition, all patients meeting ACG criteria for BE screening will also meet AGA criteria, but some patients meeting AGA criteria do not meet those of ACG. [b]Chi-square *P* value. *P* values are from comparison of the ACG to AGA non-ACG groups.

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; BE, Barrett esophagus; EGD, esophagogastroduodenoscopy; SIM-EGJ, specialized intestinal metaplasia of the esophagogastric junction.

are presented in a forest plot and sorted by risk cohort (Figure 3). The BE detection rate exceeded the performance goal of 10.6% in all risk cohorts (denoted by the dotted vertical line) but was highest in the group meeting the ACG screening criteria (28.9%). Overall, the diagnostic yield of EGD was increased 2.4- to 2.7-fold with positive EG triage.

A similar analysis was performed for risk factor–specific cohorts within the study population, namely obesity, male sex, chronic GERD, history of BE/EAC in a first-degree relative, and age greater than 50 years. For all cohorts, the BE detection rate was significantly higher than the performance goal of 10.6%. Except in the case of positive family history, the BE detection rate was

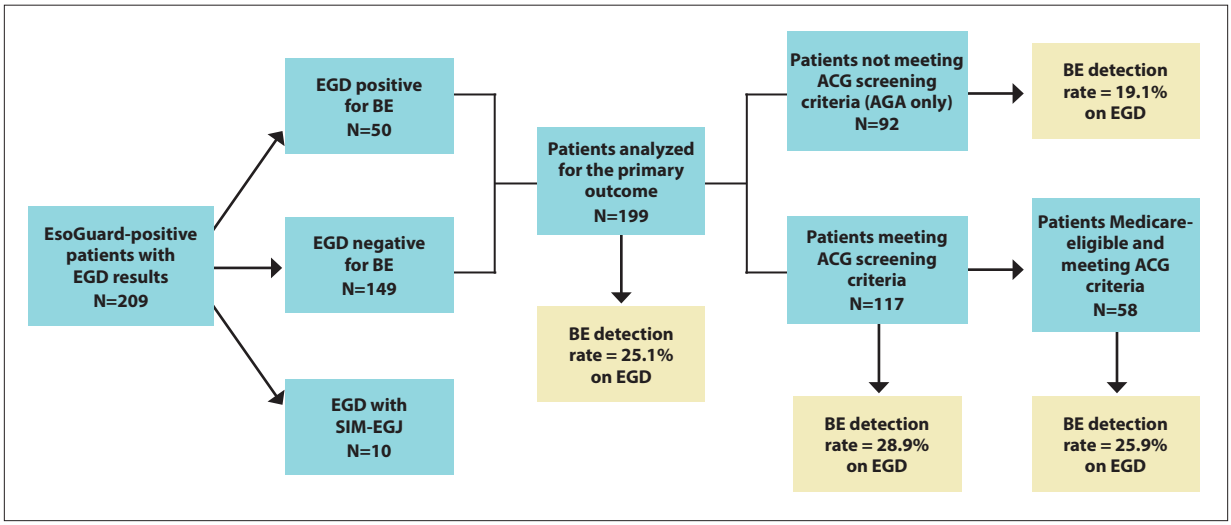

Figure 2. Patient distribution into study cohorts and associated EGD-based outcomes.

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; BE, Barrett esophagus; EGD, esophagogastroduodenoscopy; SIM-EGJ, specialized intestinal metaplasia of the esophagogastric junction.

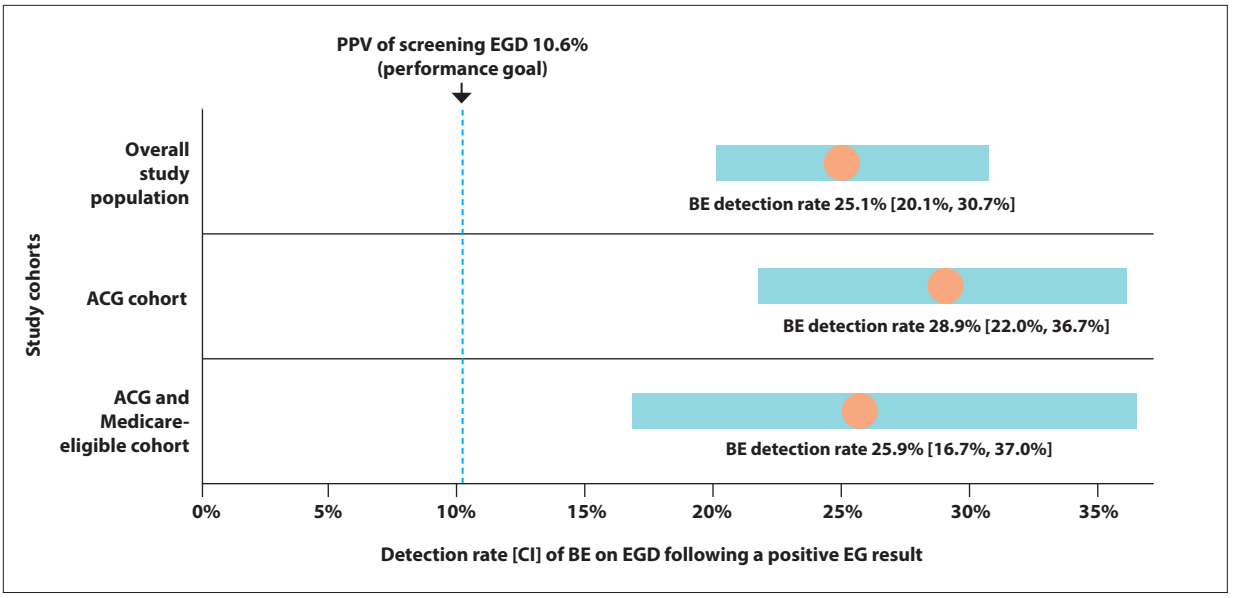

Figure 3. Diagnostic yield of EGD after a positive EG result in key study cohorts. The diagnostic yield of EGD performed in the EG-positive population is represented for each cohort by the BE detection rate. The detection rate represents the positive yield of EGDs performed after a positive EG result. The dotted line denotes the 10.6% performance goal for all study cohorts, representing the estimated diagnostic yield of screening EGD alone. This is based on US BE prevalence from a recent meta-analysis.[21] The Medicare-aged cohort includes patients 65 years and older.

ACG, American College of Gastroenterology; BE, Barrett esophagus; EG, EsoGuard; EGD, esophagogastroduodenoscopy; PPV, positive predictive value.

significantly higher than the literature-established disease prevalence for each respective risk group (Figure 4).[22]

Discussion

To our knowledge, we present the first real-world data supporting the hypothesis that diagnostic yield of EGDs performed for BE and EAC screening can be significantly enhanced by first triaging patients with EG, a nonendoscopic biomarker assay. In our hypothesis, we set a performance goal of 10.6% for the BE detection rate; this was based on published disease prevalence in the US GERD population, which serves as a surrogate for the diagnostic yield of screening EGD alone.[21] BE was detected in 25.1% of our study population and in 28.9% of the cohort specifically meeting ACG screening criteria. These were, respectively, 2.4-fold and 2.7-fold increases above the performance goal. Our findings are consistent with the EG and EGD outcomes seen in a single-center study by Greer and colleagues, which focused on BE/EAC screening in 124 veterans meeting ACG guideline criteria. At the Cleveland VA Medical Center, disease prevalence was 12.9%, and the diagnostic yield of EGD increased 2.5-fold among patients who first tested positive on EG.[17] This suggests that EG, when used for triage, can enrich the population undergoing EGD and potentially guide more efficient utilization of endoscopy resources.

We propose that the US population's BE prevalence is a reasonable surrogate for the diagnostic yield of screening EGD, although it should be noted that in reality only approximately 10% of individuals meeting the risk criteria for BE screening ever undergo endoscopic evaluation.[14] Low rates of primary care referrals, patient access and logistical barriers, and fear of the EGD procedure are all contributory.[23,24] Thus, although our data suggest that EG triage may increase the diagnostic yield of EGD 2.4- to 2.7-fold, the real impact on improving disease detection could be much higher. In contrast to the less than 10% of at-risk patients who undergo EGD as a first-line screening test, we estimate that up to 90% of patients would be willing to undergo EG. This is supported by survey data from tested patients, where greater than 90% reported willingness to repeat EG/EsoCheck if clinically indicated, and greater than 90% stated that they would recommend this approach to others.[18] Data from an ongoing registry demonstrate that patients with positive EG results are reliably being referred for EGD as a follow-up step, thus maximizing opportunities for definitive diagnosis.[15] By improving accessibility and compliance with screening, EG has potential to increase current rates of BE detection, although larger population-based studies would be required to quantify the extent.

While the highest BE detection rates were in the cohort meeting the ACG criteria for BE screening, 21.5%

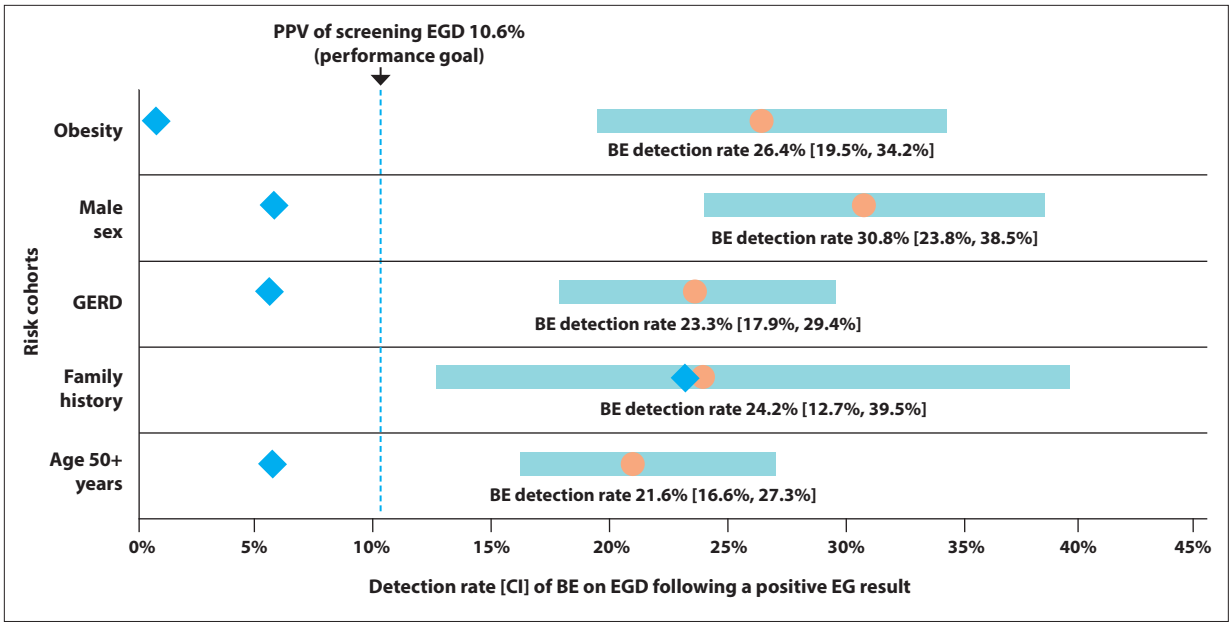

Figure 4. Diagnostic yield of EGD after a positive EG result in study cohorts with specific risk factors. The diagnostic yield of EGD performed in the EG-positive population is represented for each cohort by the BE detection rate. The detection rate represents the positive yield of EGDs performed after a positive EG result. The blue diamonds denote disease prevalence for each risk population based on published meta-analysis data, serving as a surrogate for the diagnostic yield of screening EGD alone. Prevalences are as follows: obese, 1.9%; male sex, 6.8%; chronic GERD, 6.2%; family history of BE or EAC in a first-degree relative, 23.4%; age 50 years or older, 6.1%.[22] The dotted line denotes the study's 10.6% performance goal.

BE, Barrett esophagus; EAC, esophageal adenocarcinoma; EG, EsoGuard; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; PPV, positive predictive value.

(45/209) of patients diagnosed with BE did not have chronic GERD. Indeed, the presence of chronic GERD was not proportionally higher in patients diagnosed with BE compared with those who were negative on EGD (Table 1). This further supports the AGA's stance that mandating chronic GERD as a prerequisite for BE screening may be overly restrictive.[13] Medicare-aged patients within the ACG cohort had a slightly lower detection rate at 25.9% (vs 28.9%), which could be owing to lower assay specificity in the elderly, as suggested by Moinova and colleagues; EG specificity was 76% in patients older than 61 years and 81% in those younger.[19] The cause may be age-related DNA hypermethylation on CpG islands of certain genes, which is known to occur in a nonstochastic manner.[25] A study of colonic mucosa suggested that aging could be a major contributor to the hypermethylation seen in cancer.[26] Regardless, the detection rate in the Medicare-aged ACG cohort was 2.5 times higher than the performance goal, indicating that EG triage still has benefit in older individuals. Compared with screening EGD alone, the number needed to test with EG to detect each additional case of BE would be 6.5 in the Medicare-aged ACG cohort and 5.5 in the overall ACG cohort.

Most disease (84%) detected in our study population was nondysplastic BE (NDBE), consistent with the literature where NDBE accounts for 70% to greater than 90% of the BE population.[21,27] Indefinite for dysplasia and low-grade dysplasia (LGD) accounted for 10%, and high-grade dysplasia (HGD) accounted for 6% of cases, which align with the 11.5% LGD and 5.1% HGD reported from a large multicenter consortium.[27] We found no cases of EAC, but this would be expected based on a prevalence of 0.6% in the US GERD population.[21] This suggests that the study population was representative of the real-world BE population and reduces concern for selection bias, which can often arise from retrospective data collection.

Our study has several limitations. First, BE/EAC risk factors were incomplete for 17 patients. We also took a conservative approach when categorizing patients into the ACG and AGA cohorts, and unless a risk factor was specifically documented as present, it was inferred as absent. Thus, the number of patients meeting the ACG guideline criteria may have been underestimated, particularly if ordering providers were not exhaustive in their documentation. However, the consistency of our findings with those of Greer and colleagues is reassuring.[17] A second limitation is the study's rather small sample size compared with the overall commercial volume. The risk of sampling bias cannot be eliminated, although the geographic distribution of the patients suggests that our

data arose from a relatively random subset of all those tested. This geographic distribution mirrors the broader US population distribution, with higher numbers along either coast. Finally, although we believe that in-office EG testing should significantly improve patient access and compliance with BE screening, the study was not specifically designed to evaluate this. Additional studies with larger sample sizes would be necessary, preferably with the inclusion of rural and underserved populations.

Conclusion

In summary, EGDs performed in EG-positive patients diagnosed BE at a 2.4- to 2.7-fold higher rate than would have been expected based on the diagnostic yield of screening EGD alone. This suggests that EG triage enriches the population undergoing EGD for BE. The increased BE detection rate was greatest in the cohort meeting ACG guideline criteria for screening. Compared with EGD alone as the sole screening tool, EG biomarker testing may help direct more efficient use of endoscopy resources to improve disease detection in at-risk patients.

Funding

This research was funded by Lucid Diagnostics.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Western Copernicus Group Institutional Review Board (study number: 1371531; IRB tracking number 20240954).

Informed Consent Statement

The protocol for this retrospective study was submitted to the Institutional Review Board and met requirements for a waiver of consent under 21 CFR 50.22.

Disclosures

Dr Kurland, Dr Patel, Dr Englehardt, Dr Foutz, and Dr Bradley have no financial conflicts of interest to disclose. Dr Dezfoli has served as a consultant for Lucid Diagnostics and speaker for Castle Biosciences, Phathom Pharmaceuticals, and RedHill Biopharma. Dr Tseng has served as a speaker for Castle Biosciences and Lucid Diagnostics. Dr Eghterafi has served as a speaker for Lucid Diagnostics. Dr Lee, Dr Verma, and Dr deGuzman are executives and shareholders at Lucid Diagnostics. Dr Aklog is an executive, board member, and shareholder at Lucid Diagnostics.

References

1. Runge TM, Abrams JA, Shaheen NJ. Epidemiology of Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterol Clin North Am*. 2015;44(2):203-231.
2. Cameron AJ, Ott BJ, Payne WS. The incidence of adenocarcinoma in columnar-lined (Barrett's) esophagus. *N Engl J Med*. 1985;313(14):857-859.
3. Cancer stat facts: esophageal cancer. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/esoph.html. Accessed June 2024.
4. Rubenstein JH, Sawas T, Wani S, et al. AGA Clinical Practice Guideline on Endoscopic Eradication Therapy of Barrett's Esophagus and Related Neoplasia. *Gastroenterology*. 2024;166(6):1020-1055.
5. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med*. 2009;360(22):2277-2288.
6. Shaheen NJ, Greenwald BD, Peery AF, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. *Gastrointest Endosc*. 2010;71(4):680-685.
7. Shaheen NJ, Overholt BF, Sampliner RE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. *Gastroenterology*. 2011;141(2):460-468.
8. Shaheen NJ, Falk GW, Iyer PG, et al. Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline. *Am J Gastroenterol*. 2022;117(4):559-587.
9. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. *Am J Gastroenterol*. 2022;117(1):27-56.
10. Yadlapati R, Gyawali CP, Pandolfino JE; CGIT GERD Consensus Conference Participants. AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review. *Clin Gastroenterol Hepatol*. 2022;20(5):984-994.e1.
11. Hu Q, Sun TT, Hong J, Fang JY, Xiong H, Meltzer SJ. Proton pump inhibitors do not reduce the risk of esophageal adenocarcinoma in patients with Barrett's esophagus: a systematic review and meta-analysis. *PLoS One*. 2017;12(1):e0169691.
12. Brusselaers N, Engstrand L, Lagergren J. Maintenance proton pump inhibition therapy and risk of oesophageal cancer. *Cancer Epidemiol*. 2018;53:172-177.
13. Muthusamy VR, Wani S, Gyawali CP, Komanduri S; CGIT Barrett's Esophagus Consensus Conference Participants. AGA Clinical Practice Update on New Technology and Innovation for Surveillance and Screening in Barrett's Esophagus: Expert Review. *Clin Gastroenterol Hepatol*. 2022;20(12):2696-2706.e1.
14. Kamboj AK, Katzka DA, Iyer PG. Endoscopic screening for Barrett's esophagus and esophageal adenocarcinoma: rationale, candidates, and challenges. *Gastrointest Endosc Clin N Am*. 2021;31(1):27-41.
15. Englehardt R, Samarasena JB, Bildzukewicz NA, et al. Real world experience and clinical utility of Esoguard® - interim data from the Lucid registry. *J Gastro & Digestive Systems.* 2023;7(2):43-53.
16. Lister D, Fine A, Maheshwari S, et al. Clinical utility of EsoGuard® on samples collected with EsoCheck® as a triage to endoscopy for identification of Barrett's esophagus – interim data from the CLUE study. *Arch Clin Biomed Res*. 2023;7(6):626-634.
17. Greer KB, Blum AE, Faulx AL, et al. Nonendoscopic screening for Barrett's esophagus and esophageal adenocarcinoma in at-risk veterans. *Am J Gastroenterol*. 2025;120(3):545-553.
18. 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):eaao5848.
19. Moinova HR, Verma S, Dumot J, et al. Multicenter, prospective trial of nonendoscopic biomarker-driven detection of Barrett's esophagus and esophageal adenocarcinoma. *Am J Gastroenterol*. 2024;119(11):2206-2214.
20. Spechler SJ, El-Serag HB. Why has screening and surveillance for Barrett's esophagus fallen short in stemming the rising incidence of esophageal adenocarcinoma? *Am J Gastroenterol*. 2023;118(4):590-592.
21. Saha B, Vantanasiri K, Mohan BP, et al. Prevalence of Barrett's esophagus and adenocarcinoma with and without gastroesophageal reflux: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2024;22(7):1381-1394.e7.
22. Qumseya BJ, Bukannan A, Gendy S, et al. Systematic review and meta-analysis of prevalence and risk factors for Barrett's esophagus. *Gastrointest Endosc*. 2019;90(5):707-717.e1.
23. Kolb JM, Chen M, Tavakkoli A, et al. Patient knowledge, risk perception, and barriers to Barrett's esophagus screening. *Am J Gastroenterol*. 2023;118(4):615-626.
24. Kolb JM, Chen M, Tavakkoli A, Singal AG, Vajravelu RK, Wani S; SCREEN-BE Study Group. Understanding compliance, practice patterns, and barriers among gastroenterologists and primary care providers is crucial for developing strategies to improve screening for Barrett's esophagus. *Gastroenterology*. 2022;162(6):1568-1573.e4.
25. Pal S, Tyler JK. Epigenetics and aging. *Sci Adv*. 2016;2(7):e1600584.
26. Christensen BC, Houseman EA, Marsit CJ, et al. Aging and environmental exposures alter tissue-specific DNA methylation dependent upon CpG island context. *PLoS Genet*. 2009;5(8):e1000602.
27. Desai M, Lieberman DA, Kennedy KF, et al. Increasing prevalence of high-grade dysplasia and adenocarcinoma on index endoscopy in Barrett's esophagus over the past 2 decades: data from a multicenter U.S. consortium. *Gastrointest Endosc*. 2019;89(2):257-263.e3.