Barrett High-Grade Dysplasia and Early Esophageal Adenocarcinoma in Patients With Positive Results on a Nonendoscopic Methylated DNA Biomarker Test

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Abstract: Barrett esophagus (BE) is the precursor for esophageal adenocarcinoma (EAC), with an at-risk screening population clearly defined by gastroenterology society guidelines. BE with high-grade dysplasia (HGD) and early EAC are actionable diagnoses, where endoscopic eradication therapy (EET) is effective in avoiding progression to invasive EAC. EsoGuard (EG) is a methylated DNA biomarker assay performed on esophageal cells collected nonendoscopically with EsoCheck (EC) to facilitate in-office BE screening. This case series presents 4 cases of HGD/early EAC diagnosed in patients who first tested positive on EG. Case presentations: Two patients met American College of Gastroenterology guideline criteria for BE screening, and 2 lacked chronic gastroesophageal reflux disease (GERD) but met other risk criteria. The patients with chronic GERD had well-controlled symptoms on proton pump inhibitors, and none of the patients had ever previously undergone screening for BE with esophagogastroduodenoscopy (EGD). All 4 patients underwent confirmatory EGD after receiving positive EG results, with HGD diagnosed on biopsy specimens. All patients were subsequently referred to advanced endoscopists for EET, during which time a T1a lesion was identified in 1 patient's endoscopic mucosal resection specimen. All achieved complete disease eradication after EET. Conclusion: These cases demonstrate EG/EC as an in-office nonendoscopic triage test that facilitated the timely diagnosis and subsequent treatment of HGD/early EAC in 4 patients who would otherwise not have undergone screening EGD and would have been at risk for progression to EAC. EG/EC allows BE screening in nonspecialized facilities and may be a reasonable option for patients who have not already been referred for endoscopy.

Keywords
Barrett esophagus, high-grade dysplasia, methylated biomarker, radiofrequency ablation, cryoablation, EsoGuard

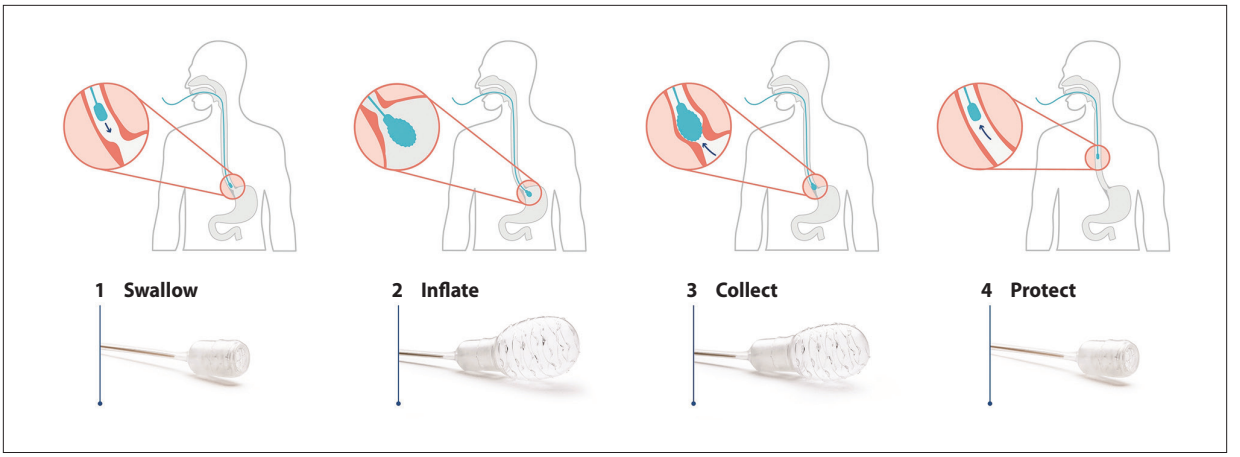


Figure 1. Illustrated step-by-step EsoCheck device administration.

Barrett esophagus (BE) is the established precursor to esophageal adenocarcinoma (EAC), the most common esophageal cancer in the United States. EAC is frequently diagnosed at an advanced stage and has poor prognosis (5-year survival rate of <25%).[1] Both BE and EAC share several well-defined risk factors, including chronic gastroesophageal reflux disease (GERD), male sex, White race, age over 50 years, tobacco smoking, obesity, and a family history of either BE or EAC in a first-degree relative.[2,3] BE with high-grade dysplasia (HGD) represents a critical point in neoplastic progression, with an annual risk of progression to EAC estimated at 5% to 8%.[4] Early identification and treatment of HGD is essential, as randomized controlled trials have demonstrated that endoscopic eradication therapy (EET) significantly reduces progression to EAC, achieving up to 90% relative risk reduction compared with surveillance alone.[5,6] According to recent estimates from the National Cancer Institute, approximately 22,370 new cases of esophageal cancer and 16,130 related deaths were seen in 2024, underscoring the importance of BE detection and early intervention.[1] However, despite the well-established risk factors and availability of effective treatment, it is estimated that only approximately 10% of patients at elevated risk for BE undergo endoscopic screening.[7,8] This low uptake is likely multifactorial, driven by underreported or unrecognized GERD symptoms, patient aversion to screening esophagogastroduodenoscopy (EGD), and limited familiarity with BE screening guidelines among primary care providers.[9,10] To improve access and uptake of screening, the American College of Gastroenterology (ACG) updated its guidelines to include nonendoscopic cell collection paired with biomarker-based testing as an acceptable alternative to endoscopy; additionally, the American Gastroenterological Association (AGA) discussed the utility of these new technologies in its 2022 clinical practice update.[2,3] One such technology is EsoGuard (EG; Lucid Diagnostics), a methylated DNA biomarker assay commercially available as a laboratory-developed test. EG is performed on samples collected using EsoCheck (EC; Lucid Diagnostics), a swallowable, US Food and Drug Administration 510(k)-cleared balloon-catheter device. The assay is conducted in a Clinical Laboratory Improvement Amendments–certified, College of American Pathologists–accredited, and New York State–licensed laboratory (LucidDx Labs).

This case series presents 4 patients diagnosed with HGD/early EAC following a positive EG test result. All 4 individuals were otherwise unlikely to undergo endoscopic screening. The timely identification of HGD/early EAC led to curative treatment with EET, with all patients achieving complete eradication of BE on follow-up endoscopy. These cases highlight the potential clinical utility of nonendoscopic screening in facilitating early detection and treatment in at-risk individuals.

EsoCheck Cell Collection and EsoGuard Assay

EC enables in-office nonendoscopic esophageal cell collection without sedation. The procedure (Figure 1) is safe, rapid (<3 minutes), and well tolerated.[11,12] Samples are shipped at ambient temperature to LucidDx Labs for analysis with EG, a methylated DNA assay that uses targeted next-generation bisulfite sequencing and a proprietary algorithm to detect aberrant methylation at 31 loci on the *VIM* and *CCNA1* genes. Clinical validation studies have shown sensitivity of 88% to 92% and negative predictive value of 99% for detection across the full BE to EAC disease spectrum.[11,13] Specificity and positive predictive value range from 72% to 81% and 30% to 33%, respectively.[11,13] Test results are binary—positive or negative—based on validated methylation thresholds. A

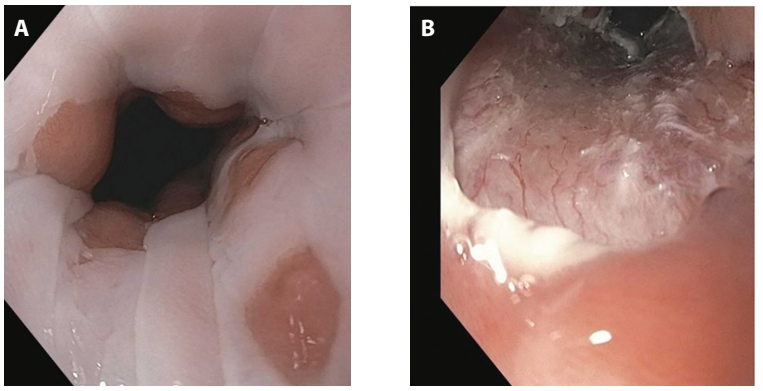


Figure 2. A: Irregular squamocolumnar junction with 2 small patches of nodularity in a 48-year-old EsoGuard-positive patient meeting American College of Gastroenterology risk criteria for Barrett esophagus screening (Case #2). **B:** Distal esophagus following endoscopic mucosal resection.

positive result indicates methylation patterns associated with BE or EAC but does not distinguish disease stage. Patients with positive results are referred to EGD for direct visualization of the esophagus and biopsies (as clinically indicated) for confirmation and staging of disease. Negative patients are unlikely to have BE or EAC and are typically managed medically, with follow-up determined by age and risk factors at the time of testing.

Case Presentations

Cases #1 and #2: Patients Meeting American College of Gastroenterology Guideline Criteria for Barrett Esophagus Screening

Two patients—both White males and former smokers with at least 5 years of GERD symptoms—underwent EG/EC testing in the outpatient primary care setting. Case #1 was 70 years old. Case #2 was 48 years old and had central obesity as an additional risk factor. Neither had previously been referred for EGD, as their GERD symptoms were well controlled with proton pump inhibitors (PPIs). Case #1 proactively requested testing after seeing an educational flyer in his physician's office. Case #2 was offered EG testing by his nurse practitioner owing to his chronic GERD and prolonged PPI use.

Cases #3 and #4: Patients Meeting American Gastroenterological Association Recommendations for Barrett Esophagus Screening

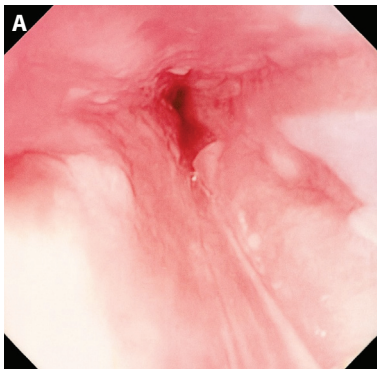
Unlike the ACG, the AGA does not define chronic GERD symptoms as a prerequisite for BE screening eligibility. This approach reflects data indicating that more than 50% of patients with prevalent EAC do not report frequent GERD symptoms and would therefore be missed under ACG screening criteria.[3]

Two additional patients—one White male aged 63 years (Case #3) and one White female aged 63 years (Case #4)—met BE risk criteria without GERD symptoms. Case #3 had a history of occupational exposure to smoke, fire, asbestos, and other potential carcinogens and was tested with EG/EC during a department-sponsored wellness event. Case #4 was an obese smoker (40 pack/year smoking history; 1 pack/day) and expressed interest in EG testing after discussion with her physician during a follow-up visit for her 29-year history of Crohn's colitis (on sulfasalazine and infliximab infusions). Neither patient had a history of chronic GERD, and neither had previously been offered endoscopic BE screening.

Diagnostic Results

All 4 patients received positive EG results, which were followed by EGD for direct visualization of the esophagus. Case #2 was noted to only have an irregular Z-line and 2 areas of nodularity immediately above the Z-line (Figure 2A). The squamocolumnar junction was biopsied in all 4 quadrants owing to the positive biomarkers, as were the nodular regions. The maximum length of salmon-colored mucosa in Case #3 was noted to measure 2.5 cm and also included a small nodule. Case #1 and Case #4 had maximum disease lengths of 10 cm and 5 cm, respectively. Representative images from Case #4 are shown in Figure 3A and 3B.

Histopathology demonstrated BE with HGD in all 4 patients. Case #2 was referred to a tertiary care center for endoscopic mucosal resection (EMR; Figure 2B), with the final pathology showing T1a adenocarcinoma. Three months after resection, the patient underwent radiofrequency ablation (RFA) of residual BE. The patient demonstrated no evidence of disease on 3-month follow-up EGD, with continued absence of disease on subsequent EGD at 6 months.



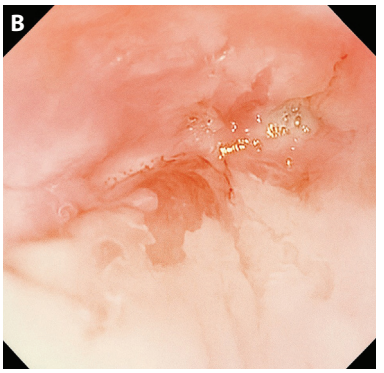


Figure 3. A: Abnormal distal esophageal mucosa suggestive of Barrett esophagus in an EsoGuard-positive patient meeting American Gastroenterological Association risk criteria for screening, with biopsies demonstrating histopathology of high-grade dysplasia (Case #4). **B:** Proximal extension of the columnar epithelium with a Prague score of C2M5.

Case #3 also underwent EMR, with final pathology confirming HGD. This was followed by 3 sessions of RFA. Case #1 underwent 5 sessions of RFA. Both patients achieved complete disease eradication, as confirmed on 3-month follow-up EGD.

Case #4 underwent cryoablation approximately 4 weeks after her initial diagnosis, but follow-up EGD at 8 weeks revealed residual Barrett mucosa covering approximately 40% of the original segment. Second and third treatments were performed at 12 weeks and 36 weeks, respectively. After the third treatment, complete macroscopic eradication of the Barrett epithelium was observed. Follow-up EGD performed at 48 weeks after the initial treatment confirmed complete eradication of the intestinal metaplasia.

Discussion

This case series reports 4 real-world cases of HGD/early EAC initially identified through nonendoscopic BE screening using the EC cell collection device and the EG methylated DNA assay. All patients underwent uncomplicated in-office EC collection, and positive EG results prompted EGD—a diagnostic evaluation that none had previously been referred to. These cases highlight an important gap in BE screening and the potential of nonendoscopic tools to close it. BE progresses to EAC and proceeds through stages of nondysplastic BE (NDBE) to low-grade dysplasia (LGD) and HGD.[14] In patients with HGD, EET is strongly recommended over surveillance, given the high risk of progression to EAC.[15] HGD confers the highest risk of progression to EAC with annual progression rates of 5% to 8% per year, although some studies have reported the rate to be as high as 11.8%.[4,16,17] LGD carries a lower progression risk (~1.5% per year), and a patient-centered approach is recommended where either EET or intensive surveillance may be considered.[15,17] NDBE, which constitutes approximately 80% of BE cases,[18] has the lowest cancer risk but requires routine surveillance endoscopy every 3 to 5 years to detect incident dysplasia or cancer.[2] Importantly, BE and its dysplastic stages are asymptomatic and cannot be distinguished without diagnostic testing, underscoring the need for effective screening and surveillance strategies.[14]

Despite guideline recommendations, fewer than 10% of at-risk individuals undergo screening EGD, leaving many cases of BE and dysplasia undetected.[7,8] To address this gap, the ACG and AGA have included nonendoscopic solutions as alternatives to traditional screening EGD.[2,3] Tests such as EG offer a safe, rapid, and minimally invasive triage to EGD that can be administered in primary care settings, even by nonphysicians, thereby improving accessibility and uptake of BE screening. Although this case series is limited by its small sample size, it illustrates the practical value of EG/EC in detecting clinically actionable disease among patients who would not have otherwise undergone EGD—particularly those without chronic GERD symptoms. All 4 patients were promptly referred for diagnostic EGD, diagnosed with HGD/early EAC, and treated with EET, achieving complete eradication of intestinal metaplasia.

Conclusion

This case series demonstrates the potential role of EG/EC as a triage tool to EGD for BE screening. The integration of nonendoscopic testing into routine care enabled timely identification and treatment of HGD/early EAC in patients unlikely to be screened through conventional pathways. These cases also demonstrate the ease with which EG/EC can be integrated into clinical care to support screening and enhance disease detection.

Statement of Ethics

The plan for publishing this case series was submitted to the WIRB-Copernicus Group Institutional Review Board (IRB), which provided approval, and the Board found that the research meets requirements for a waiver of consent under 21 CFR 50.22 (IRB approval number 20244575).

Funders

Lucid Diagnostics

Data Availability Statement

The data that support the findings of this case series are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Disclosures

Dr Kurland, Dr Stellern, and Dr Kachwalla have no relevant conflicts of interest to disclose. Dr Wani has served as a consultant for Exact Sciences, Castle Biosciences, Lucid Diagnostics, Cyted, and Boston Scientific; and has received research support from Lucid Diagnostics, CDx Diagnostics, Exact Sciences, and Cyted. Dr Verma, Dr Lee, and Dr Aklog are employees of Lucid Diagnostics and hold stock or stock options in the company.

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