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Nonendoscopic Detection of Barrett Esophagus and Esophageal Adenocarcinoma: Recent Advances and Implications

Prasad G. Iyer, MD, MSc,
Mayo Clinic, Rochester, Minnesota

David A. Katzka, MD
Mayo Clinic, Rochester, Minnesota

Esophageal adenocarcinoma (EAC) is a lethal form of cancer with poor prognosis (5-year survival ≤20% when diagnosed after the onset of symptoms), and its incidence has rapidly increased over the last 4 decades (1). Barrett esophagus (BE), a metaplastic change of the esophageal squamous to intestinalized columnar epithelium, is the only known precursor for EAC. In some individuals, BE may progress to EAC through the development of low- and high-grade dysplasia. Endoscopic therapy for dysplasia can reduce the risk for progression to EAC, and endoscopic treatment of early-stage EAC is associated with excellent long-term survival. Therefore, consideration of endoscopic screening for BE in patients with chronic reflux and other risk factors (age >50 years, male sex, White race, smoking, and family history of BE or EAC) followed by endoscopic surveillance for detecting dysplasia or early-stage EAC is recommended by professional societies (2). Surveillance is shown to detect earlier stage EAC and modestly improve EAC mortality in retrospective studies (3).

However, this strategy has failed to adequately alter the rising incidence or mortality rates of EAC. In fact, 90% of patients with EAC continue to be diagnosed outside screening and surveillance programs despite the presence of BE in 60% of EACs at diagnosis. Several reasons may underlie this. First, 40% to 50% of patients with EAC lack heartburn symptoms, a key criterion incorporated into most society screening guidelines. Second, only 10% to 15% of individuals at risk for BE have endoscopic evaluation, which is currently essential to diagnosing BE (4). Third, sedated endoscopy is invasive, is expensive, and can be performed only by trained endoscopists who are limited in number. As a result, a paradigm shift in strategies for BE screening and early detection of dysplasia or EAC is needed.

Corresponding Author: Prasad G. Iyer, MD, MSc, Professor of Medicine, Division of Gastroenterology and Hepatology Mayo Clinic, 200 1st Street SW, Rochester, MN 55905; iyer.prasad@mayo.edu.
Current Author Addresses: Drs. Iyer and Katzka: Division of Gastroenterology and Hepatology Mayo Clinic, 200 1st Street SW, Rochester, MN 55905.
Author Contributions: Conception and design: P.G. Iyer.
Analysis and interpretation of the data: P.G. Iyer.
Drafting of the article: P.G. Iyer, D.A. Katzka.
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Minimally invasive nonendoscopic esophageal sampling devices combined with molecular markers to detect BE and early-stage EAC are being developed in order to mitigate limitations of the current approach. Among these, the best studied include string-attached, capsuleen-closed, compressed spherical pieces of polyurethane foam that deploy in the stomach 5 minutes after swallowing (Cytosponge TFF3 test [Medtronic GI Solutions], EsophaCap [CapNostics]) or a balloon that is inflated after swallowing and is inverted and withdrawn via an attached cord (EsoCheck [Lucid Diagnostics]). These devices provide esophageal cytology samples, which are analyzed for biomarkers associated with BE and EAC, such as immunehistochemically detected trefoil factor 3 (TFF3, a protein marker of intestinalized epithelium) or methylated DNA markers. These swallowable esophageal cell collection devices can be administered by a nurse in an office setting (with procedure times ≤10 minutes) and do not require sedation.

The performance characteristics of these tests have been largely evaluated in case–control studies done in referral populations, with reported test sensitivities of 80% to 94% and specificities of 62% to 94% (5–7). The true sensitivity and specificity of these nonendoscopic tests in general screening populations in the primary care setting are yet to be established. Notably, more than 90% of patients can successfully swallow these cell collection devices, and more than 80% of trial participants undergoing both endoscopy and the capsule sponge test prefer the capsule sponge test (5). Although most are not commercially available yet, these tests are anticipated to be substantially less expensive than sedated endoscopy. Modeling studies have also suggested the potential cost-effectiveness of these minimally invasive tests compared with no screening, when used in a population at highest risk for BE and EAC (50-year-old White men with chronic reflux) (8).

In a large community-based clinical trial, patients with chronic reflux who were treated with proton-pump inhibitor therapy for at least 6 months from primary care practices in the United Kingdom were randomly assigned to the Cytosponge-TFF3 test or usual management (with endoscopic evaluation only if thought appropriate clinically) (9). Of almost 1800 patients completing the Cytosponge-TFF3 test, 240 had positive results, 140 of whom had BE on confirmatory endoscopy (positive predictive value, 61%). Nine patients had dysplasia and 5 had stage 1 EAC: These patients were successfully managed endoscopically. In the usual care group, only 13 were diagnosed with BE and 3 with advanced-stage EAC. Hence, this test not only increased BE diagnosis 10-fold but also identified early-stage EAC and dysplasia, demonstrating the rationale of such a minimally invasive molecular test in a high-risk primary care population.

By increasing access and participation (due to reduced test burden), these minimally invasive tests could lead to increased rates of BE and EAC detection. Although current recommendations suggest screening only in patients with chronic reflux, given that 40% to 50% of those with BE and EAC deny chronic reflux symptoms, minimally invasive BE screening technology will likely allow expansion of screening to those without reflux (but with other risk factors). Nevertheless, the potential benefits of this expanded approach will have to be balanced with the risk for increased false-positive test results and patient anxiety, medical expenses for confirmatory testing, and potential adverse effects from endoscopic

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evaluation. The strategy must include careful consideration of the life expectancy and comorbid conditions of the patient.

These tests will likely be implemented in primary care clinics as an office-based test administered by a nurse, given that first-line management of reflux is usually handled in primary care. A positive nonendoscopic test result would be followed by confirmatory endoscopy; hence these nonendoscopic tests are complementary to the endoscopic diagnosis of BE and subsequent detection of dysplasia. Widespread implementation will need high throughput scaling of the assay technology and other logistics, in conjunction with a commercial partner, education of providers on the indications for and implications of screening using these novel minimally invasive technologies, training of medical personnel in the safe administration of the test, and reimbursement of the test by payers (both Medicare and commercial). Establishing the real-world performance characteristics in screening populations and cost-effectiveness of these approaches as well as their ability to reduce EAC incidence and mortality will also be critical in enhancing adoption. Implementation of the test in practice could be facilitated by the incorporation of artificial intelligence–powered BE/EAC risk assessment algorithms in electronic medical records, which could “flag” patient charts for such tests in an attempt to increase utilization. Furthermore, innovative methods for dysplasia detection in BE, including improvements in mucosal sampling and advanced imaging or artificial intelligence approaches in combination with biomarkers, will need to be paired with improved risk prediction of progression to EAC in patients with BE but without dysplasia to increase the effectiveness of endoscopic surveillance.

In conclusion, encouraging progress in the nonendoscopic detection of BE will potentially lead to a more complete identification of those at risk for EAC and, when paired with improved dysplasia detection and risk prognostication, could lead to meaningful advances in EAC outcomes, an elusive goal for many decades.

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