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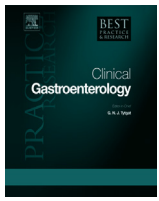

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# Molecular biomarkers added to image-enhanced endoscopic imaging: Will they further improve diagnostic accuracy?

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A B S T R A C T

Barrett's esophagus (BE) is a premalignant condition for esophageal adenocarcinoma (EAC) which has dismal prognosis. The risk of progression from BE to EAC increases with dysplasia grade. The purpose of surveillance exams in BE is to detect dysplasia at an early stage and intervene before development of EAC. However, the current surveillance practices have not been effective in reducing EAC incidence. Major limitations of this strategy include challenges in identifying dysplasia during endoscopic surveillance, which leads to sampling error and subjectivity in the histological diagnosis of dysplasia due to interobserver variation amongst pathologists. Advanced imaging techniques may allow targeted biopsy of suspicious foci with incremental yield in dysplasia detection and reduce sampling error. Molecular biomarker panels have the potential to objectively assess progression risk without the subjectivity associated with histology. Combining molecular markers with advanced imaging appears to be a promising strategy to further improve risk stratification and reduce EAC incidence and mortality. Few studies have investigated this strategy so far and the results are promising. Further research on different permutations between the available biomarkers and imaging techniques will help us determine the best possible combination that detects dysplasia with high sensitivity and specificity. Further

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research is needed to establish the combined strategy's cost effectiveness and feasibility.



## Introduction

Barrett's esophagus (BE) is a premalignant condition in which the normal squamous epithelium lining the lower esophagus is replaced by metaplastic columnar epithelium [1]. BE is the strongest risk factor for esophageal adenocarcinoma (EAC) [2]. The absolute risk of EAC in BE patients is low at 0.5% or less annually but the relative risk is 30–40 times higher than general population. The incidence of EAC has increased in the western world by six-fold over the past four decades [3]. EAC has a dismal five year survival rate of less than 20% [4]. The increasing trend of EAC incidence despite current surveillance protocols to detect dysplasia or early neoplasia in BE patients, suggests that the current strategies are not effective.

Most GI societies recommend surveillance endoscopy every 3–5 years for BE with no dysplasia and on an annual basis for BE with low grade dysplasia [5–7]. The purpose of surveillance is to detect dysplasia or neoplasia at an early stage and intervene before it progresses to EAC. Standard surveillance endoscopy consists of a thorough examination with white light endoscopy (WLE) followed by targeted biopsies of any suspicious lesions and random four quadrant biopsies every 1–2 cm of BE segment (Seattle protocol) [8]. Dysplastic lesions typically occur in small foci and could be missed despite biopsying diligently [9]. Performing multiple biopsies prolongs the procedure duration and this could explain the low compliance with recommendations in practice settings [10]. Together, these lead to missed dysplasia. Even after successful biopsying of a dysplastic focus, there could be considerable disagreement between pathologists with regard to confirming dysplasia and assessing the degree of dysplasia [11–15].

With the advent of effective and safe endoscopic therapeutic options like RFA and EMR for treatment of BE related dysplasia, there is growing interest in developing alternate strategies to obtain targeted tissue samples and improve risk stratification. Image-enhanced endoscopic (IEE) imaging can help detect small foci of dysplasia, which might be missed with WLE [16,17] but does not solve the issue of interobserver disagreement between pathologists. Recent studies have identified molecular biomarkers that have the potential to predict progression and detect dysplasia [12]. However, the accuracy of biomarkers is dependent on the biopsied sample. The next logical step would be to combine molecular biomarkers with targeted biopsies using IEE imaging to improve detection of high risk lesions in BE. This review will focus on exploring the pros and cons of advanced imaging and molecular biomarkers and the role combining them to improve outcomes.

## Advances in endoscopic imaging

Currently, standard screening and surveillance endoscopies for BE in most institutions are performed using high-resolution WLE and high-definition (HD) monitors. This provides excellent visualization of the esophageal mucosa and allows sampling of BE mucosa for histopathology [18,19]. However, the current surveillance recommendations have not decreased EAC incidence so far and this has led to concerns on its cost-effectiveness.

There are several possible explanations for this failure. The experience of an endoscopist plays an important role in detecting visible mucosal abnormalities [18]. Experienced endoscopists can detect visible lesions in up to 80% of BE patients referred for work up of high grade dysplasia (HGD) or intramucosal cancer (IMC) without visible lesions on prior exams [20,21]. In the absence of visible lesions, random four quadrant biopsies are still recommended per the Seattle protocol [5]. However, the biopsying protocol samples only about 5% of BE mucosa with inherent risk of missing small dysplastic foci [18]. Also, endoscopists' compliance with Seattle protocol is suboptimal as the biopsying